RANDOMISED CONTROL TRIAL OF I.V LEVETIRACETAM VS. FOSPHENYTOIN IN TERMS OF THEIR EFFECTIVENESS IN STATUS EPILEPTICUS

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations of

The award of the degree of

M.D IN PEDIATRIC MEDICINE

BRANCH VII

THANJAVUR MEDICAL COLLEGE,

THANJAVUR - 613 004.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032.

MAY 2018

CERTIFICATE

I certify that the dissertation titled "**RANDOMISED CONTROL TRIAL OF I.V LEVETIRACETAM VS. FOSPHENYTOIN IN TERMS OF THEIR EFFECTIVENESS IN STATUS EPILEPTICUS",** submitted by **Dr.KOWSIK.M,** for the degree of DOCTOR OF MEDICINE (PAEDIATRICS) (BRANCH VII), to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is the result of original research work undertaken by him in the Department of Paediatrics, Thanjavur Medical College, Thanjavur.

Prof Dr .S. RAJASEKAR. MD., DCH,
Professor and HOD of pediatrics,
Department of pediatrics,
Thanjavur medical college,
Thanjavur.

Dr. P. SELVAKUMAR MD.,
Associate professor of pediatrics,
Department of pediatrics,
Thanjavur Medical College,
Thanjavur.

Place: Thanjavur
Date:

DEAN
Thanjavur Medical College,
Thanjavur.

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA - 613001

(Affiliated to the T.N.Dr.MGR Medical University, Chennai)

INSTITUTIONAL ETHICAL COMMITTEE

CERTIFICATE

Approval No. : 377

This is to certify that The Research Proposal / Project titled

RANDOMISED CONTROL TRIAL OF LEVETIRACETAM Vs IV FOSPHENYTOIN IN TERMS OF THEIR EFFECTIVENESS IN STATUS EPILEPTICUS

submitted by Dr. M. KONSIK **of**

Dept. of PAEDIATRICS **Thanjavur Medical College, Thanjavur**

was approved by the Ethical Committee.

Thanjavur

Dated : 01.03.2017

THANJAVUR MEDICAL COLLEGE ETHICAL COMMITTEE THANJAVUR-4

Secretary
Ethical Committee
TMC, Thanjavur.

THE SECRETARY
INSTITUTIONAL ETHICAL COMMITTEE
THANJAVUR MEDICAL COLLEGE,
THANJAVUR.

URKUND

Urkund Analysis Result

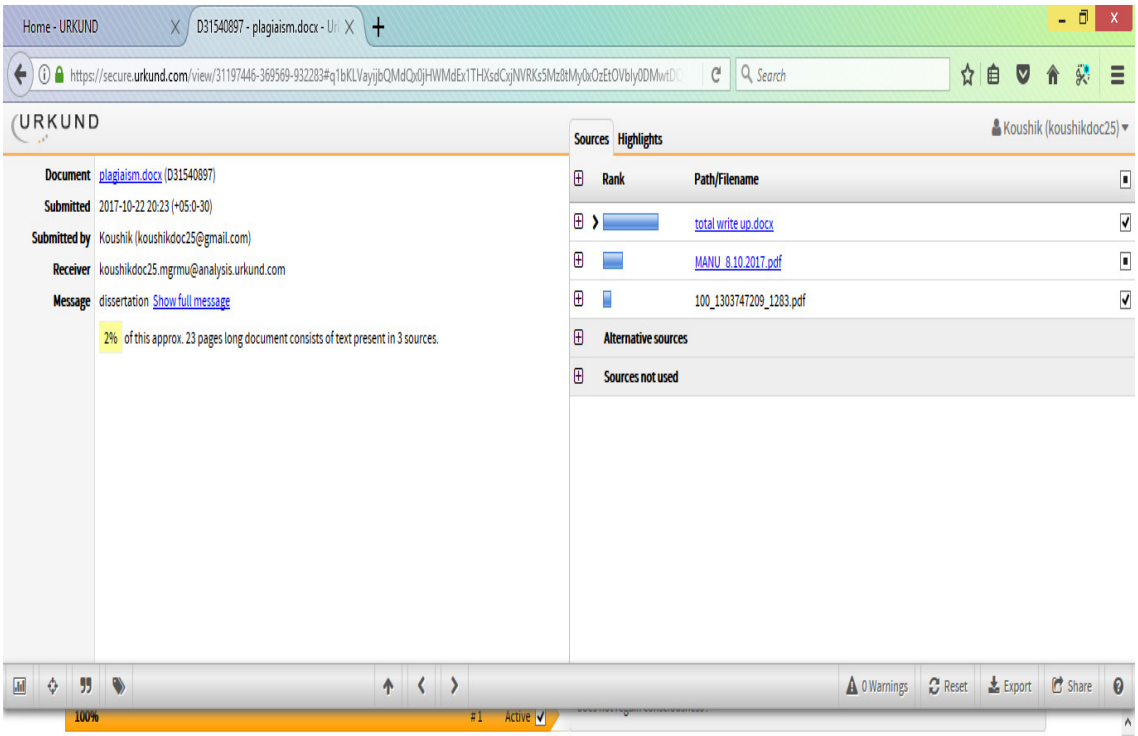
Analysed Document: plagiaism.docx (D31540897)
Submitted: 10/22/2017 4:53:00 PM
Submitted By: koushikdoc25@gmail.com
Significance: 2 %

Sources included in the report:

total write up.docx (D31180599)
100_1303747209_1283.pdf (D22077584)
MANU_8.10.2017.pdf (D31108868)

Instances where selected sources appear:

9



Status Epilepticus is a common medical neurological emergency associated with high morbidity; if not, associated with mortality [2] As an initial treatment, potent gamma-butyric agonists such as benzodiazepines will be administered to stop the child's convulsions. Lorazepam and Diazepam are commonly used as first line drugs. They are short acting drugs which produce immediate effects. A long acting anticonvulsant drug is necessary to prevent recurrent convulsions. Phenytoin and Phenobarbitone were frequently used to treat status epilepticus in children. After the development of fosphenytoin, it is recommended as a second line therapy but both phenytoin and fosphenytoin can cause blood pressure reduction and arrhythmias. Levetiracetam is another antiepileptic effective against status epilepticus, which is associated with lower incidence of adverse effects. [3] The purpose of this study was to determine whether intravenous Fosphenytoin or intravenous Levetiracetam is a better second line anticonvulsant based on efficacy and safety for treatment of convulsive Status Epilepticus in pediatric population.

REVIEW OF LITERATURE HISTORICAL BACKGROUND DEFINITION OF SEIZURE :

CERTIFICATE – II

This is to certify that this dissertation work titled **"RANDOMISED CONTROL TRIAL OF I.V LEVETIRACETAM VS. FOSPHENYTOIN IN TERMS OF THEIR EFFECTIVENESS IN STATUS EPILEPTICUS**" of the candidate **Dr.KOWSIK.M** with registration number **201517204** for the award of **DOCTOR OF MEDICINE** in the branch of **PEDIATRICS(Branch VII)** .I personally verified the urkund.com website for the purpose of plagiarism check. I found that uploaded thesis file contains from introduction to conclusion pages and result shows **2** percentage of plagiarism in the dissertation.

DECLARATION

I hereby solemnly declare that the dissertation titled "**RANDOMISED CONTROL TRIAL OF I.V LEVETIRACETAM VS. FOSPHENYTOIN IN TERMS OF THEIR EFFECTIVENESS IN STATUS EPILEPTICUS",** has been prepared by me under the guidance of **Dr.P.SELVAKUMAR. M.D.,** ASSOCIATE PROFESSOR, DEPARTMENT OF PEDIATRICS THANJAVUR MEDICAL COLLEGE, THANJAVUR. This is submitted to THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement for the degree of DOCTOR OF MEDICINE (PAEDIATRICS) (BRANCH VII).

Place: Thanjavur

Date: Signature

ACKNOWLEDGEMENT

I am extremely grateful to my guide **DR.SELVAKUMAR.P, MD,** Associate Professor**,** Department of pediatrics, Thanjavur medical college, for his scholarly guidance during my study and postgraduate period.

I gratefully acknowledge and express my sincere thanks to **Prof. Dr. JEYAKUMAR M.S, Mch**, Dean, Thanjavur Medical College and hospital, Thanjavur. for allowing me to do this dissertation and utilize the institutional facilities.

I am extremely grateful to **Prof. Dr. RAJASEKAR. MD., DCH.,** professor and HOD, Department of pediatrics Thanjavur medical college, Thanjavur for his full-fledged support during my post graduate period.

I express my gratitude to my respected Co-guide, Assistant professor **Dr.C.S.SENTHIL KUMAR, MD., DCH, & Dr.N.ARAVIND THIRUGNANASAMBANDHAM** for their scholarly guidance and valuable time they has rendered to do this work effectively.

I would also like to extend my warm gratitude to all the Assistant Professors for their constant encouragement and support.

I would like to thank all my colleagues, juniors and friends who have been a constant source of encouragement to me. Special thanks to all the children and their parents who whole heartedly co-operated and participated in this study.

Last but not the least, I would like to express my most sincere gratitude to Dr.MUTHUKUMARAN, Dr.MAHESHWARAN, Dr.SHREE JAYASUDHA, Dr.RAMESH PRASATH and Dr.ARUNEESHWAR for their help and constant support for this thesis.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Status epilepticus is defined as a seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness.[1]

Status Epilepticus is a common medical neurological emergency associated with high morbidity; if not, associated with mortality [2]

As an initial treatment, potent gamma-butyric agonists such as benzodiazepines will be administered to stop the child's convulsions. Lorazepam and Diazepam are commonly used as first line drugs. They are short acting drugs which produce immediate effects. A long acting anticonvulsant drug is necessary to prevent recurrent convulsions. Phenytoin and Phenobarbitone were frequently used to treat status epilepticus in children. After the development of fosphenytoin, it is recommended as a second line therapy but both phenytoin and fosphenytoin can cause blood pressure reduction and arrhythmias.

Levetiracetam is another antiepileptic effective against status epilepticus, which is associated with lower incidence of adverse effects. [3]

The purpose of this study was to determine whether intravenous Fosphenytoin or intravenous Levetiracetam is a better second line anticonvulsant based on efficacy and safety for treatment of convulsive Status Epilepticus in pediatric population.

REVIEW OF LITERATURE

DEFINITION OF SEIZURE :

A seizure is defined as transient occurrence of signs and symptoms due to abnormal excessive synchronous neuronal activity in brain.[4]

STATUS EPILEPTICUS

CLASSICAL DEFINITION:

Status epilepticus is classically defined as "condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief interval so as to produce an enduring and unvarying epileptic condition".[5]

ILAE DEFINITION

Status epilepticus is a condition resulting either from failure of the pathway responsible for termination of seizure or from the initiation , which lead to prolonged seizure (after time point t1). It is a condition, which may have long term consequences (after time point t2) including neuronal injury , alteration of neuronal network and neuronal injury , depending on duration and type of seizure[6].

TABLE 1 - TWO OPERATIONAL DIMENSIONS IN STATUS EPILEPTICUS [6]

S.No	TIME POINT	OPERATIONAL DIMENSION	TIME IN CONVULSIVE SE	TIME IN FOCAL SE
1	After t1	*Seizures should be regarded as " continuous seizure activity" *It indicates when treatment should be initiated	5 min	30 min
2	After t2	*It indicates when long term consequences may appear.	10 min	>60 min

(t1 - time point 1; t2 - time point 2)

INDIAN ACADEMY OF PEDIATRICS[1]

Status Epilepticus (SE): A seizure lasting more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness.

Operational Definition*: Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to >5 min of (i) continuous seizures or (ii) two or more discrete seizures between which there is incomplete recovery of consciousness.

Refractory SE: Seizures persist despite the administration of two appropriate anticonvulsants at acceptable doses, with a minimum duration of status of 60 minutes by history or on observation.

Super-Refractory SE: SE that continues 24 hours or more after the onset of anesthesia, including those cases in which the status epilepticus recurs on the reduction or withdrawal of anesthesia.

Operational definition is used for the purpose of initiating treatment.[1]

BURDEN

The annual incidence of status epilepticus ranges from 9.9-41 per 10000 / year with peaks in pediatric population and elderly[7]

The burden of disease, estimated using DALY, accounts for 1% of the total burden of disease in the world. The annual economic burden of seizure disorder in our country is 0.5% of GNP [8].

Incidence of status epilepticus is more in poor population. Its prevalence is higher in rural (1.9%) compared with the urban population(0.6%).[8] In children the etiology is usually acute central nervous system infection .

According to an UK study, majority of cases of status epilepticus occur in children who are previously neurologically normal. Around quarter of the cases of status epilepticus are due to prolonged febrile seizures and 17% of them are acutely symptomatic [9].

RISK FACTORS FOR REFRACTORINESS [10]:

- Non convulsive status epilepticus
- Hyperglycemia at presentation
- Low Glasgow coma scale
- Focal motor seizures at onset.

CLASSIFICATION

BASED ON SEMIOLOGY [6]

TABLE 2 – CLASSIFICATION OF SEIZURES BASED ON SEMIOLOGY

	MOTOR ACTIVITY	DEGREE OF IMPAIRED CONSIOUSNESS
A	With prominent motor activity	A1 - Tonic clonic SE A2 - Myoclonic SE A3 - Focal motor SE
B	Without prominent motor activity	B1 - NCSE with coma B2 - NCSE without coma

BASED ON EEG:

Various factors to be scored are location, name of pattern, morphology, time related features, modulation and effect of intervention on EEG.[6]

BASED ON ETIOLOGY [6]:

TABLE 3 CLASSIFICATION OF SEIZURES BASED ON ETIOLOGY

1	Acutely symptomatic	Seizures due to head injury, hypoxemia, hypoglycemia, acute infection, electrolyte imbalance, drug withdrawal or intoxication
2	Remote symptomatic	Seizures secondary to static illness (remote cerebral insult in neonatal period)
3	Progressive encephalopathy	Status epilepticus in children with progressive CNS disorder (lipid storage disease, mitochondrial disorder, Rasmussen encephalitis)
4	Cryptogenic status epilepticus	Without any identifiable etiology

FEBRILE STATUS EPILEPTICUS

- It is a separate entity.
- It is the most common type of SE in children.[4]
- Febrile illness is the only provocation for status epilepticus. It should be considered after excluding direct CNS infection.

BASED ON AGE [6]:

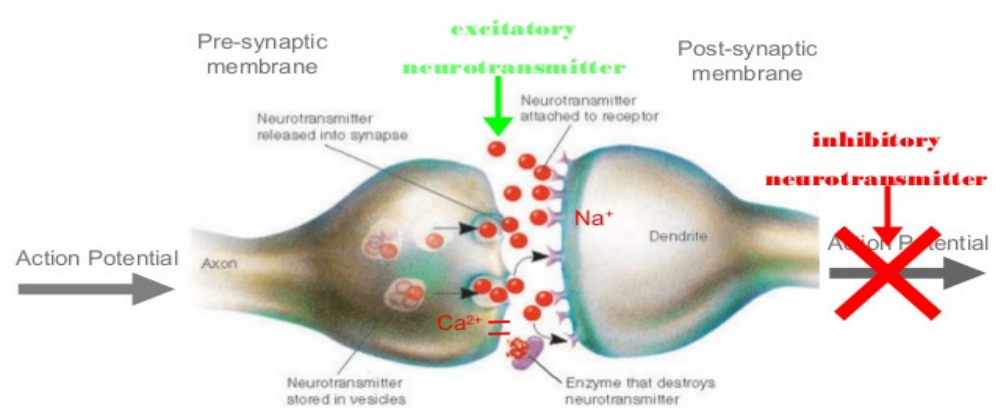
- Neonatal (< 30 days)
- Infancy
- Childhood (2- 12 years)
- Adolescence
- Elderly (above 60 years)
-

PATHOPHYSIOLOGY :

TABLE 4 – NEUROTRANSMITTERS IN SE [4]

Sustained Seizures are due to reduced inhibition and increased excitation based on neuro- chemical levels.		
1	Excitatory neurotransmitter	Glutamate is the most common one and NMDA (N-Methyl D Aspartate) receptor is involved
2	Inhibitory neurotransmitter	GABA (Gamma Amino Butyric Acid) is the common inhibitory neurotransmitter.

FIGURE 1 – PATHOPHYSIOLOGY OF STATUS EPILEPTICUS



Status epilepticus results in both neuronal necrosis and apoptosis. Apoptosis occurs as a result of increase in pro-apoptotic factors(like apoptosis inducing factor, BAX protein and ceramide) and intracellular calcium.[4]

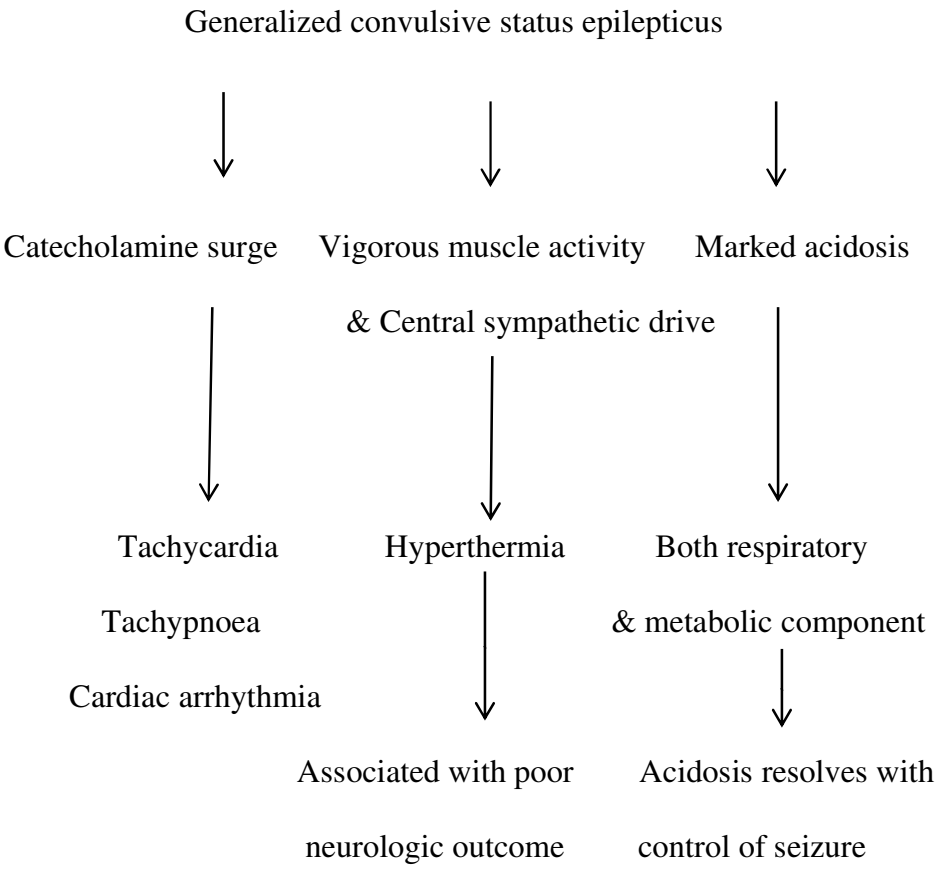
PGE2 can raise glutamate release and lower potassium current which eventually lead to increased excitability.[4]

Sustained seizures reduce GABA inhibition progressively. At receptor level GABAnergic pathway fails and seizures become resistant to pharmacotherapy[4]

OTHER MALADAPTIVE CHANGES:

- Depletion of inhibitory neuropeptides like galanin , somatostatins and neuropeptide in hippocampus.[11]
- Reduction of chloride gradient across neuronal membrane[11]
- Increase in expression of substance P and tachykinins[11]

PHYSIOLOGICAL CHANGES IN STATUS EPILEPTICUS



ETIOLOGY [4]:

- New onset epilepsy of any type
- Febrile convulsion (6 months – 5 years)
- Hypoxic ischemic encephalopathy
- Infections (CNS infections-Encephalitis, Meningitis)
- Head trauma
- Metabolic causes (Hypoglycemia, Hyponatremia, Hypomagnesemia, Hypocalcemia)
- Neurodegenerative disorders
- Neurocutaneous syndrome
- Toxins(camphor, heavy metals, organophosphates)
- Medication changes →Non compliance (anti-epileptic drugs) Inadequate dosage.
- Ischemic Stroke (Arterial or Venous)
- Inborn errors of metabolism – Storage disorders
- Intracranial hemorrhage
- Systemic conditions (Hypertensive or Renal or Hepatic encephalopathy)
- Brain Tumors

Acute symptomatic status epilepticus is the most common category in pediatric population.

PROGNOSIS:

Factors that affect prognosis in children with Status Epilepticus are,

1. Type of seizure
2. Duration of seizure
3. Etiology of seizure
4. Age of the child

Type of seizure:

Focal and NCSE are associated with refractory status epilepticus[10]

Duration of seizure:

Prolonged seizures lead to hypoglycemia, hypercarbia, hypoxia and marked acidosis which eventually leads to neuronal destruction[12]

Etiology of seizure:

According to Nelgian et al, mortality is low in children classified as idiopathic and febrile Status Epilepticus [13]. Most death occurs in children with acute symptomatic and remote symptomatic causes. [14]

Age of the child:

TABLE 5 – AGE OF CHILD IN RELATION TO PROGNOSIS OF SE [15]

S. No.	Age	Sequelae rate
1	<1 year	29%
2	1-3 years	11%
3	>3 years	6%

COMPLICATIONS OF STATUS EPILEPTICUS:

1. Hypoxemia

It occurs due to impaired ventilation, excessive tracheobronchial secretion and increased oxygen consumption.

Severe hypoxia and acidosis leads to impaired myocardial contractibility, reduced stroke volume and hypotension.

2. Acidosis (both respiratory and metabolic)

3.Glucose alterations

TABLE 6 – ALTERATION OF BLOOD GLUCOSE IN SE

During early phase of status epilepticus	Massive Catecholamine release &Sympathetic surge	Hyperglycemia
Prolonged status epilepticus	Increased metabolic demand	Hypoglycemia

4. Blood pressure disturbances

BP and Heart rate rise at early phase due to massive sympathetic surge and catecholamine release, but prolonged seizures lead to decline in blood Pressure.

5. Intra Cranial Pressure

Increase in intra cranial pressure further interferes with cerebral oxygen and substrate supply. This results in cerebral edema.

Other factors that contribute to increased intra cranial pressure are hypoxemia, hypercarbia and metabolic acidosis with compensatory vasodilatation and increased blood flow to cerebrum[16]

6.Other effects

Hyperpyrexia [17]

Hyperkalemia (due to rhabdomyolysis)

Acute renal failure due to myoglobinuria and hypotension

Apnea [18]

Aspiration pneumonia

Neurogenic pulmonary edema [18]

7.Morbidity

Neurologic sequelae (Focal motor deficit [4], Intellectual deficit, Behavioral disturbances Epilepsy)

8. Mortality (3% - 9%)

DIAGNOSIS :

1. History and clinical examination using systematically designed proforma.
2. Investigations in child with status epilepticus [1]

   First line investigation

   Without previous seizure history

   1. Random blood sugar
   2. Serum sodium (especially < 6 months)
   3. Calcium (if < 2 years)

   With previous seizure history

   1. AED level

   If febrile

   1. Complete blood count

   Lumbar puncture

Refractory status epilepticus

1. Video EEG recording

Second line investigation

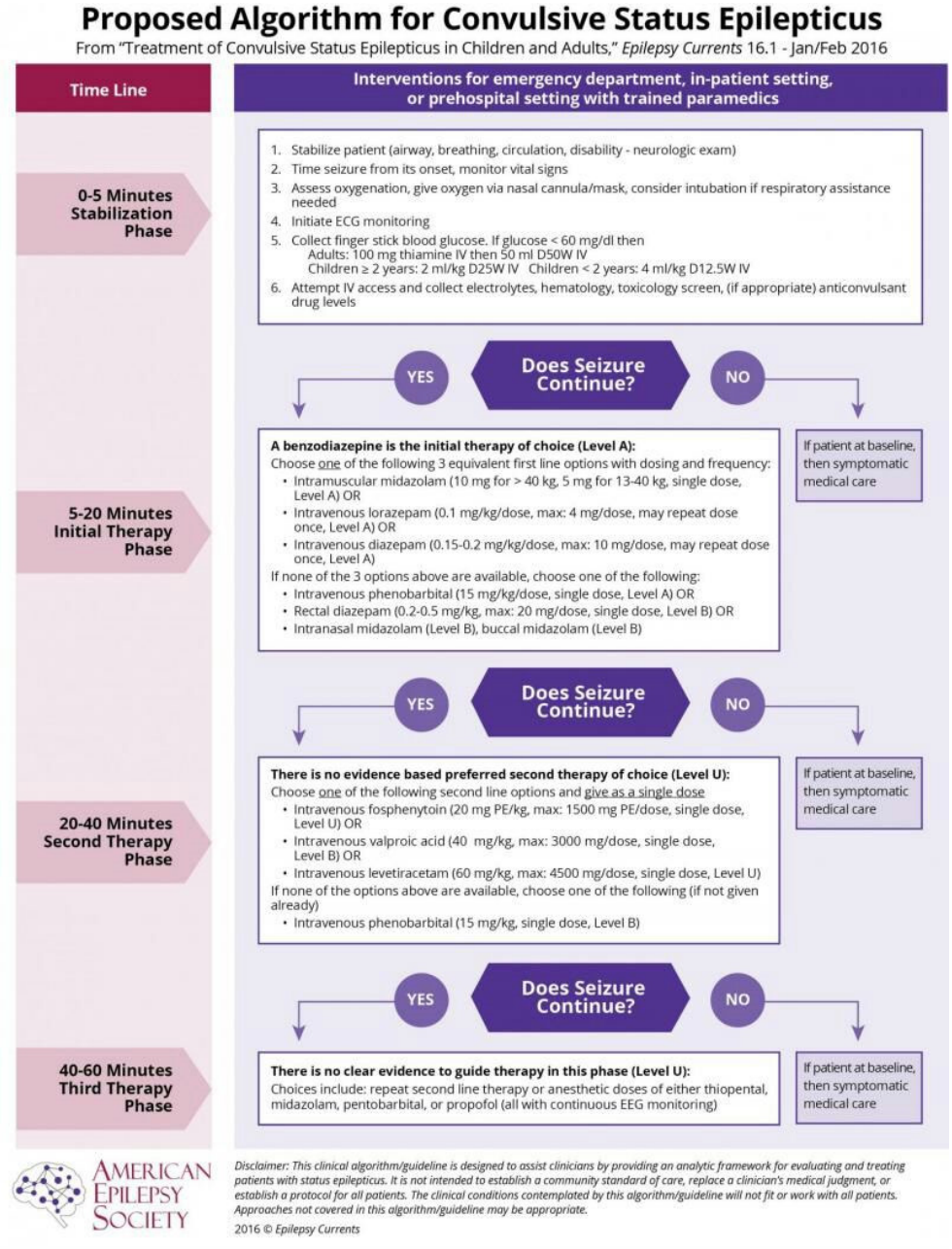
1. EEG
2. Neuro imaging (MRI is most sensitive)

Special tests

1. If history suggestive of metabolic disorder, consider metabolic and genetic testing.
2. Workup for autoimmune encephalitis.
3. Urine toxicology. (if clinical suspicion)

TREATMENT PROTOCOL

FIGURE 2 – TREATMENT OF CONVULSIVE STATUS EPILEPTICUS IN CHILDREN AND ADULTS



GENERAL MANAGEMENT OF ACUTE SEIZURES:

STABILISING THE CHILD

In the convulsing child, initial supportive, therapeutic and diagnostic measures need to be conducted simultaneously. The goal of the therapy is to stop clinical end electrical seizure activity by promptly giving appropriate drugs, in adequate doses, with attention to the possibility of complicating apnea, hypoventilation and other metabolic abnormalities.

When stabilizing the child, the main priority in management is preserving vital function. That is, protecting the airway, maintaining breathing, supporting the circulation, and correcting the metabolic derangements.

PHARMACOTHERAPY

1. **BENZODIAZEPINES :**

They are first line anticonvulsants for the treatment of SE in children.

In our study

Midazolam was the benzodiazepine of choice.

Advantages *of Midazolam:*

Increased water solubility

Shorter duration of action &

Better local tolerance when injected intravenously [19]

Route of administration :

- Buccal
- Intranasal
- Intravenous & Intramuscular.[19]

Dosage:

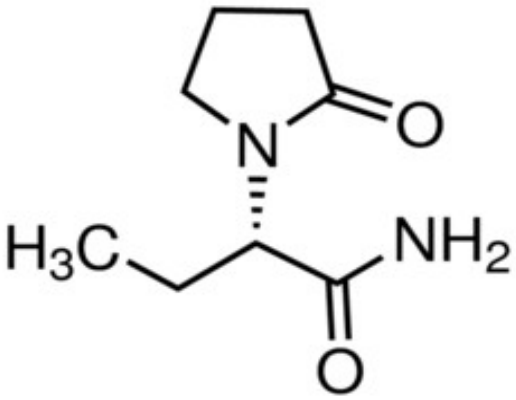
0.15 -0.2 mg/kg (max upto 5 mg) -- may repeat in 5-10 min[1]

2.LEVETIRACETAM

Chemical structure

It is the S-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine acetamide, with a molecular weight of 170.21 and the chemical formula $C_8H_{14}N_2O_2$.[20]

FIGURE 3 – CHEMICAL STRUCTURE OF LEVETIRACETAM



Mechanism of action

The proposed mechanism of levetiracetam action related to its binding to synaptic vesicle protein (SV2A) is a predominant isoform of the three known SV2 proteins [20]

Binding of the levetiracetam to SVA2 results in synaptic release of glutamate and GABA [20]

Pharmacokinetics:

Volume of distribution

0.5 to 0.7 liter per kg

Tmax :

2 - 46 months → 1.4 hr

4 - 12 years → 0.5 hr

Half-life :

2 – 46 months → 5.3 hrs

4 – 12 years → 4.9 hrs

Clearance :

2 – 46 months → 1.4 ml/min/kg

4 – 12 years → 1.12 ml/min/kg

Protein binding :

Protein binding of levetiracetam is insignifigant (<10 %).

Metabolism :

Levetiracetam biotransformation pathway is not cytochrome p450 dependent.

It has low potential for significant pharmacokinetic interaction because it's major metabolic pathway is hydrolysis and it undergoes negligible oxidative metabolism in liver. Levetiracetam does not induce or inhibit drug metabolizing enzymes[20]

Excretion :

Main route of excretion is by renal route either in administered form (66%) or as carbolic acid metabolite (pharmacologically inactive form) as a result of amide functional group hydrolysis.[20]

Dosage :

Intravenous Levetiracetam

Acceptable dose ranges from 20- 60 mg / kg can be used for convulsive status epilepticus with transient side effects even at upper limits of dose range.

Reconstitution fluids :

The suitable diluents are 0.9 % sodium chloride, 5 % dextrose & Ringer lactate.

Rate of infusion :

Rate of infusion is 5 mg / kg/min [1]

Storage :

It is stored between 20 – 25° C.

Adverse effects :

According to Oluwaseun Egunsola [21], the most common adverse event that warrants discontinuation were behavioral problems (10.9%) and somnolence (8.7%).

TABLE 7 – ADVERSE EFFECTS OF LEVETIRACETAM.

S.NO	ADVERSE EVENT	PERCENTAGE
1.	Behavioral problems	More frequent[22]
2	Fatigue	
3	Irritability	
4	Unsteadiness	
5.	Somnolence	
6	Nervousness	Less frequent[22]
4	Anorexia	
5	Anxiety	
6	Rhinitis	
7	Abnormal hepatic function	Rare
8	Dermatological problems	
9	Bone marrow suppression	

3. FOSPHENYTOIN

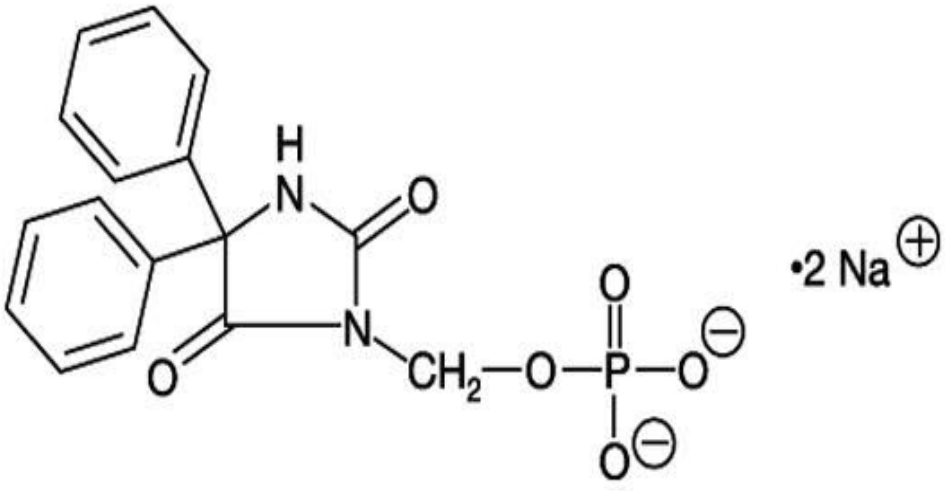
Fosphenytoin sodium is a phosphate ester, prodrug of phenytoin[23]. It was developed as replacement for phenytoin sodium.

Chemistry :

Chemical formula : $C_{16}H_{15}N_2O_6P$

Molar mass : 362.274 g/mol

FIGURE 4 - CHEMICAL STRUCTURE OF FOSPHENYTOIN



Mechanism of action :

Fosphenytion stabilizes neuronal membrane thereby prevents recurrent detonation of normal neuronal cells during depolarization shift which occurs in epileptic patients and consists of synchronous and large depolarization over which action potential is overlapped. This is brought by

prolonging the inactivated stage of voltage sensitive sodium channel which governs the refractory period of neuron. This results in inhibition of high frequency discharges with negligible effect on low frequency discharges which allows sodium channels to recover even when their inactivation is continued. This effect of fosphenytoin has been noted at therapeutic concentration[23].

Other effects like inhibition of glutamate response, facilitation of GABA response and reduction in calcium influx have been oted at toxic concentration[23]

Pharmacokinetics

The conversion half life of fosphenytoin is nearly 15 minutes. The mechanism of conversion has not been established but phosphatases play a primary role. Each mole of fosphenytoin is converted to one mole of formate, phenytoin and phosphate[24, 25]

Absorption :

Fosphenytoin has a half-life of 15 minutes following intra venous infusion. Fosphenytoin is completely bioavailable follow intramuscular administration but peak concentration occurs approximately after 30 minutes.[24,25]

Plasma fosphenytoin concentration following intramuscular administration is more sustained but lower than those following intra venous infusion because of the time required for fosphenytoin absorption from the site of injection.[24,25]

Metabolism :

Bioavailability of various market preparation may differ. Hence it is adviced to use single brand. It is 95% - 99% protein bound (especially albumin). The percentage bound is lowered as total fosphenytoin concentration increases which is aresult of the fact that binding to plasma proteins is saturable. [23]

Fosphenytoin takes the place of phenytoin in protein binding sites. Phenytoin is metabolized by glucuronide conjugation as well as by hydroxylation involving 2C19 and CYP2C9 in liver[23,24,25]

Volume of distribution :

Volume of distribution of fosphenytoin rises with dose and rate. Volume of distribution is 4.3 – 10 liters .

Excretion :

5% unchanged form is excreted in urine. [23]

Advantage of fosphenytoin over phenytoin :

Fosphenytoin is water soluble pro-drug of phenytoin that has been introduced to overcome the difficulties in intravenous phenytoin administration , which it has replaced for use in benzodiazepine-resistant status epilepticus.

Its advantages over phenytoin include more rapid intravenous infusion and lower potential for cardiac and local tissue toxicity. Fosphenytoin can be infused with both glucose and saline, but phenytoin cannot be administered in a drip of dextrose solution (because it results in precipitation)[23]

Loading dose :

Loading dose for pediatric status epilepticus is 15mg PE /kg to 20mg PE/kg[1]. In the body fosphenytoin is rapidly changed to phenytoin sodium ; it's doses are expressed in PE (phenytoin equivalents) [24,25]

Because of risk of hypotension, fosphenytoin should not be infused at a rate of more than 150 mg PE/min in children. Continuous monitoring of respiratory function, electrocardiogram and BP is mandatory[23].

Rate of infusion :

Rate of infusion is 2 – 3 mg PE/kg/min [1]

Compatible fluid :

5% dextrose and 0.9 % sodium chloride.

Concentration required is 1.5 – 25 mg PE/ml [1]

Adverse effects :

Side effects of fosphenytoin are similar to phenytoin and includes cardiac arrhythmias, hypotension, CNS adverse effects(ataxia ,dizziness, somnolence, nystagmus, diplopia)[23]

Intra venous injections result in local vascular injury(damage to intima). This eventually leads to thrombosis of vein. Hence edema and discoloration of injected limb occurs. Extravasation of solution results in tissue necrosis[23]

Fall in BP and cardiac arrhythmias occur only on intra venous injections.

Kensuke Nakamura et al concluded that levetiracetam and fosphenytoin are equally efficacious in preventing recurrent seizures after the termination of SE by benzodiapezines. Further adverse events were lower and tolerable in LEV group.[26]

Vincent Alvarez et al did a retrospective comparative study on phenytoin, levetiracetam and valproate as a second line status epilepticus treatment in adults. In this study, phenytoin failed to control SE in 41.4% patients and LEV in 48.3%. (p value is statistically in- significant)[27]

Chakravarthi S et al studied the effectiveness of LEV and FPHT in adults with regard to primary and secondary outcomes. In their study, phenytoin achieved control of seizures in 68.2% compared to 59.1% in LEV and both the groups showed comparable results with respect to recurrence of seizures, the need of ventilator support and death. They concluded that LEV may be an attractive and effective alternative to phenytoin. [28]

In the study by Manjari Tripathi et al, hypotension, respiratory depression, need of intubation, ICU care were not observed when status epilepticus was terminated with intravenous loading dose of levetiracetam.[29]

Jaclyn O Connor et al concluded in their study, Levetiracetam is as safe and effective as phenytoin for the treatment of status epilepticus with lower incidence of adverse events.[3]

In a study by Knake et al, levetiractam terminated seizure activity in all patients and is not associated with any serious adverse events. [30]

Ted Lee et al did a retrospective study on use of LEV in management of toxic seizures and concluded that LEV used as a second line anti- epileptic terminated drug induced seizures and prevented seizure recurrence without obvious adverse effects. [31]

According to Zeid Yasiry et al, the efficacy of phenytoin (50.2%) was found to be lower when compared to levetiracetam (68.5%) [32].

In a study by Bernherds R Ogutu et al on the pharmacokinetics and clinical effects of phenytoin and FPHT in children with severefalciparum malaria and SE, they found that i.v or i.m fosphenytoin offers a convinent alternative to i.v phenytoin. [25]

According to Ilo E Leppik et al's preclinical and clinical studies on phenytoin prodrug, they found that both i.v and i.m administrations of FPHT maintained stable levels of phenytoin. Both i.v and i.m FPHT were well tolerated by the patients as evidenced by the absence of serious adverse reactions. [33]

AIM AND OBJECTIVES

- To compare the efficacy of I.V Fosphenytoin with I.V Levetiracetam in a pediatric population suffering from Status Epilepticus.
- To compare the safety of Fosphenytoin with Levetiracetam in a pediatric population treated for Status Epilepticus.
- To compare the incidence of recurrence between Fosphenytoin and Levetiracetam in a pediatric population with Status Epilepticus.
- To compare the incidence of adverse reactions between Fosphenytoin and Levetiracetam when used to treat Status Epilepticus in a pediatric population.

MATERIALS AND METHODS

STUDY DESIGN:

Prospective randomized control trial

STUDY SETTING:

Govt. Rajah Mirasdar hospital.

STUDY PERIOD:

January 2017 – July 2017

STUDY POPULATION:

1 month – 12 years old children who presented to Pediatric Emergency department at Govt. Rajah Mirasdar Hospital in a convulsing state.

INCLUSION CRITERIA:

Children in age group of 1 month -12 years in whom seizure persisted after two doses of I.V Midazolam (0.15 mg/kg/dose).

EXCLUSION CRITERIA:

- Child in shock.
- Children who were previously on oral Phenytoin or oral Levetiracetam for seizure medications.
- Pre-hospital treatment records were unavailable.
- Administration of injectable AEDs (BZD, phenytoin, levetiracetam, sodium valproate) in the previous 24 hrs.

SAMPLING TECHNIQUE:

Simple random sampling

SAMPLE SIZE:

Sample size for our study was calculated using openepi.com , keeping the type 1 error (α) as 0.95 , power (β) as 0.8 , ratio of sample as 1 and mean difference (σ) as 0.5, the sample size required for each group is 25. Hence for two groups the sample required was 50.

METHODOLOGY OF COLLECTING DATA:

A written consent obtained from parents / guardian during the time of enrolment.

The study sample was divided into two groups. Children treated with Fosphenytoin constitute Group I and those who received Levetiracetam constitute Group II.

HISTORY :

- Current seizure activity : nature of onset , duration , any secondary generalization and the postictal sensorium in case the seizure has subsided.
- Presence or absence of fever, any viral prodrome, ear discharge, neck pain, irritability or any other intercurrent illnesses.
- Any prior history of seizures if present, specify if on medications, dosage and compliance.
- Features of raised intracranial tension like headache / vomiting / posturing.
- Intoxication or toxic exposure.
- Other CNS abnormality (e.g. Ventricular-peritoneal shunt, prior CNS infection)

- Birth history (e.g. anoxic encephalopathy)
- Developmental history (by using Trivandrum developmental scale where all the milestones falling to the left of the vertical line should have been achieved by the child)
- Family history of seizures

EXAMINATION:

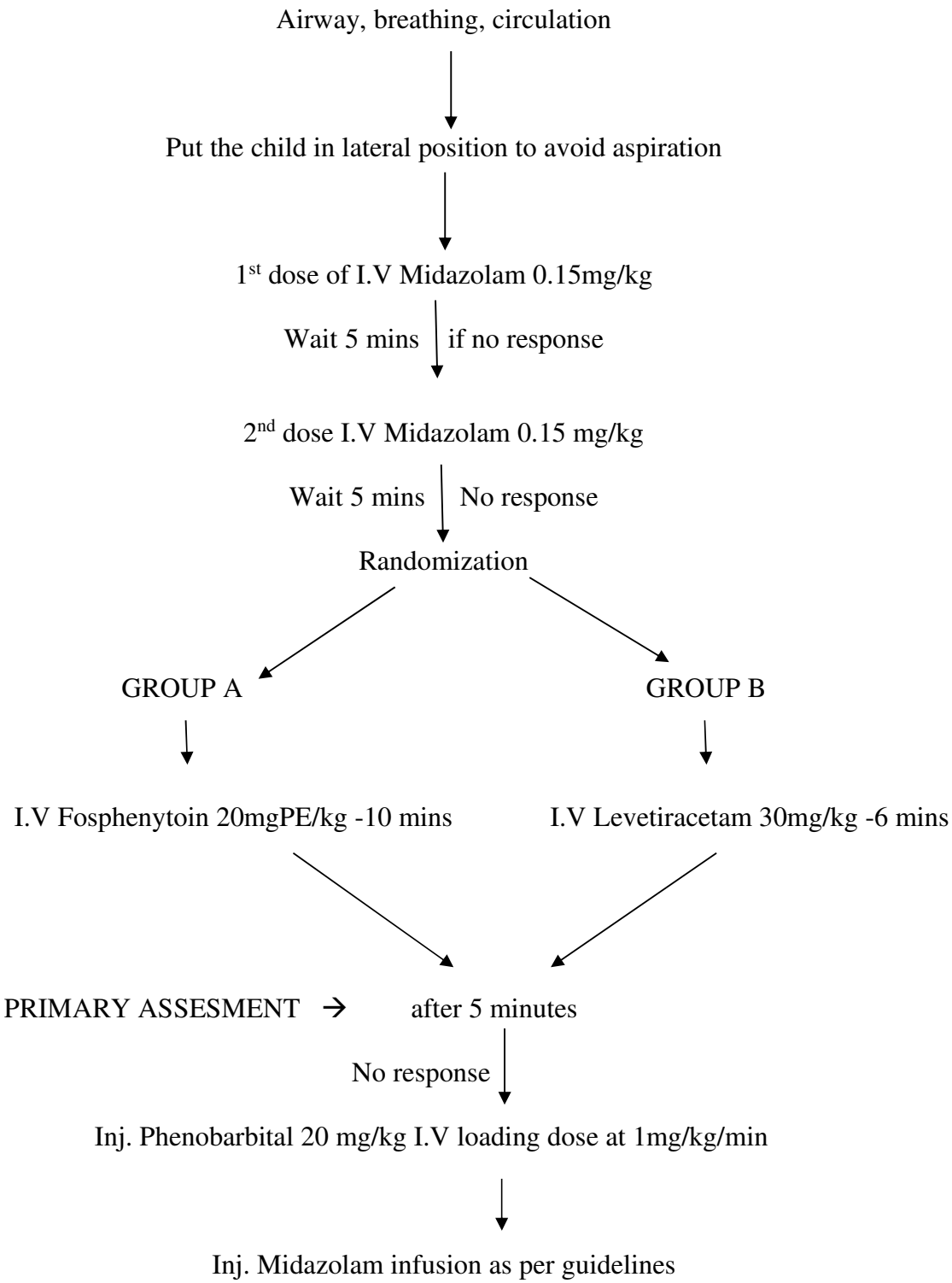
- Vital signs: temperature, heart rate, respiratory rate and the blood pressure.
- Look for features of respiratory distress, poor peripheral perfusion and the hydration status
- Note the type of seizure activity present.
- Assess for features of raised intracranial pressure.
- Also assess for possible etiology: features of meningitis, septicemia, trauma , neurocutaneous stigmata, toxin ingestion and any peculiar body odour.

LABORATORY STUDIES:

Obtain laboratory studies based on age and likely etiologies.

- Blood glucose level
- Electrolyte levels (sodium, potassium, calcium and if possible magnesium)
- Arterial blood gas analysis
- Toxicology screen (if suggestive history available)
- Complete blood count
- Renal function test
- Liver function test
- Cerebrospinal fluid examination
- Neuroimaging and Electroencephalography

STUDY FLOW-ALGORITHM:



Following drug administration, we compared both groups with the following parameters.

Primary outcome

Efficacy:

a. Whether the episode of convulsive status epilepticus was terminated with FPHT and LEV.
b. The need to use additional antiepileptic drugs to terminate the presenting convulsions
c. Time taken from administration of drug in emergency department/PICU to termination of convulsion.

Cessation of status:

Defined as cessation of status and improving mental status following administration of drugs.

Five minutes following the administration of study medication, assessment will be performed by the pediatric postgraduate.

The patient will be examined for the following:

1. Jerky movements
2. Increased tone
3. Level of consciousness

Continued seizure activity is defined as presence of either jerky movements or increased tone. If seizure activity is present, then the next anticonvulsant is to be infused as per the study protocol.

The time at which convulsive activity has ceased (as defined above) is recorded.

Secondary outcome:

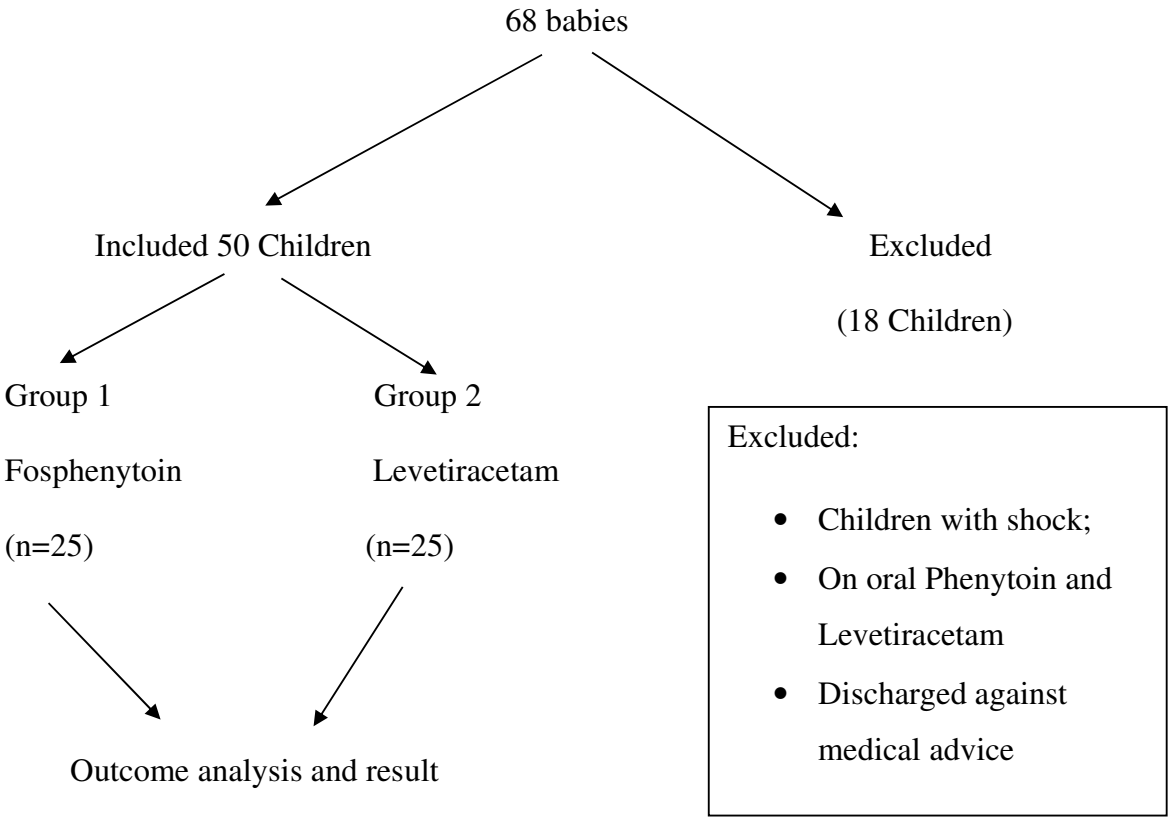
a. Whether convulsions recurred within 24 hours after termination of seizures following administration of FPHT and LEV.
b. Seizure free duration in case of recurrence.
c. Length of stay in PICU and hospital
d. Occurrence of life threatening hypotension: within 60 minutes of administration of drugs.
e. Need for intubation (within 60 minutes following study drug infusion
f. Incidence of adverse effects

(Hypotension: measured as greater than 20%reduction from baseline Respiratory depression: measured as greater than 20%reduction from baseline)

Children will be assessed daily while they remain in-patients to watch out for adverse events.

DATA ANALYSIS

68 children between the age group of 1 month to 12 years who had Status Epilepticus and presented to Pediatric Emergency department at Govt. Rajah Mirasdar hospital, Thanjavur, during the study period as shown in the figure below. Those who had Status Epilepticus that persisted after 2 bolus of BZD I.V Midazolam (0.15 mg/kg/dose) were included in this study. Children with shock; on oral Phenytoin and Levetiracetam medications; and who were discharged against medical advice were excluded from the study.



AVAILABILITY, STORAGE AND DILUTION:

- Available strength of Fosphenytoin is 75 mg PE/ ml (10 ml vial). (750 mg equivalent to 500mg of Phenytoin sodium).
- Available strength of Levetiracetam is 100 mg/ml (5 ml vial).
- Available strength of Midazolam is 1 mg/ml (5 ml vial).

STORAGE:

- Levetiracetam: It is stored at 25^{o}C (77^{o}F).
- Fosphenytoin: It is stored under refrigeration at 2-8 ^{o}C. Product has to be discarded if kept at room temperature for more than 48 hours, after reconstitution.
- Midazolam: It is stored below 25^{o}C.

DILUTION:

Commonly used diluent in our study was 0.9% sodium chloride solution for Midazolam, Levetiracetam and Fosphenytoin.

INFUSION:

Levetiracetam:

- Concentration: Required dosage + 100 ml compatible fluid.
- Rate of infusion: 5 mg/kg/min.

Fosphenytoin:

- Concentration: 1.5 – 25 mg PE/ml.
- Rate of infusion: 2 mg PE/kg/min.

STATISTICAL ANALYSIS:

Comparisons of various domains of both groups were analyzed using:

A. Mann-Whitney U test,

B. Fisher's Exact test,

C. Unpaired 't' test

Inference of 'P' value is tabulated below:

TABLE 8 – 'P' VALUE AND ITS SIGNIFICANCE

S.NO.	'P' VALUE	INTERPRETATION
1	Less than or equal to 0.01	Highly significant
2	Less than or equal to 0.05	Significant
3	More than 0.05	Not Significant

RESULTS AND ANALYSIS

BASELINE CHARACTERISTICS OF BOTH STUDY GROUP:

1) COMPARISON OF AGE IN BOTH STUDY GROUP:

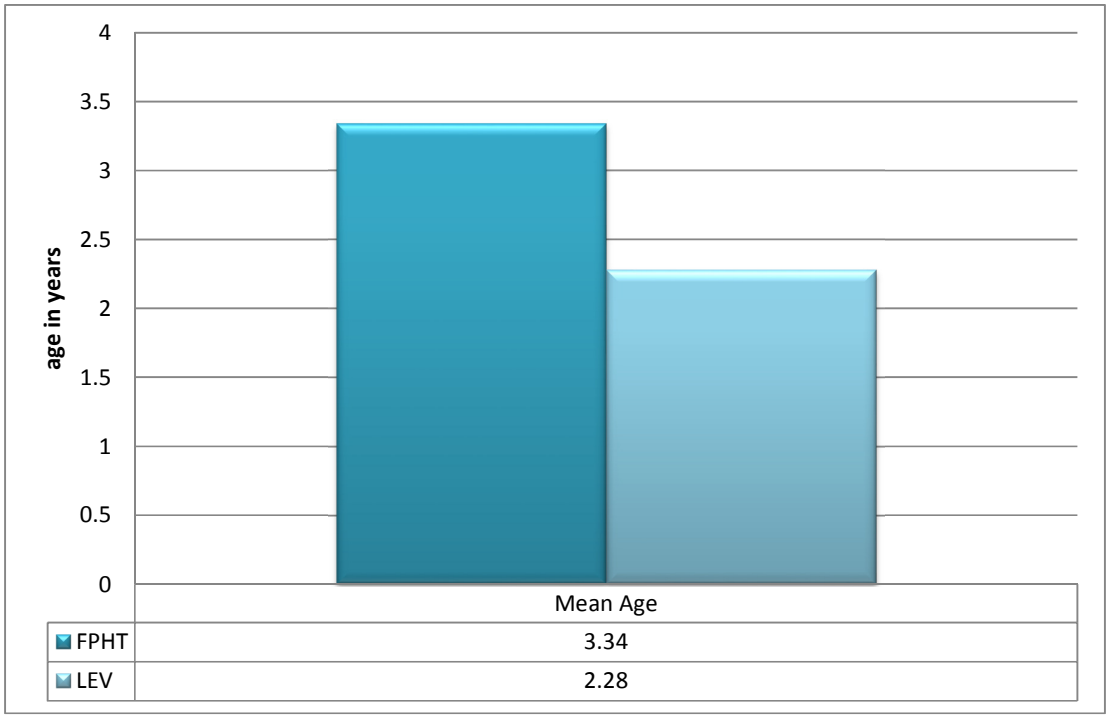
TABLE 9 - COMPARISON OF CASE DISTRIBUTION BASED ON AGE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'p' value	Statistical Test
1	Age(in years)	3.34 ± 3.6	2.28 ± 2.19	0.657(NS)	Mann-Whitney U test

Data are expressed as mean ± SD. P value less than 0.05 is considered as significant and Mann Whitney U test was used to test the significance.

Mean age in Fosphenytoin group was 3.34 ± 3.6 years whereas in Levetiracetam group, it was 2.28 ± 2.19 years which was not statistically significant ('p'= 0.657).

FIGURE 5 - COMPARISON OF CASE DISTRIBUTION BASED ON AGE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



**Data are expressed as mean ± SD.*

**The height of the bar in the vertical bar diagram represents the mean.*

**The error bar represents the standard deviation.*

**The total number of sample in each group was 25.*

2) COMPARISON OF DISTRIBUTION OF GENDER IN FPHT & LEV GROUP:

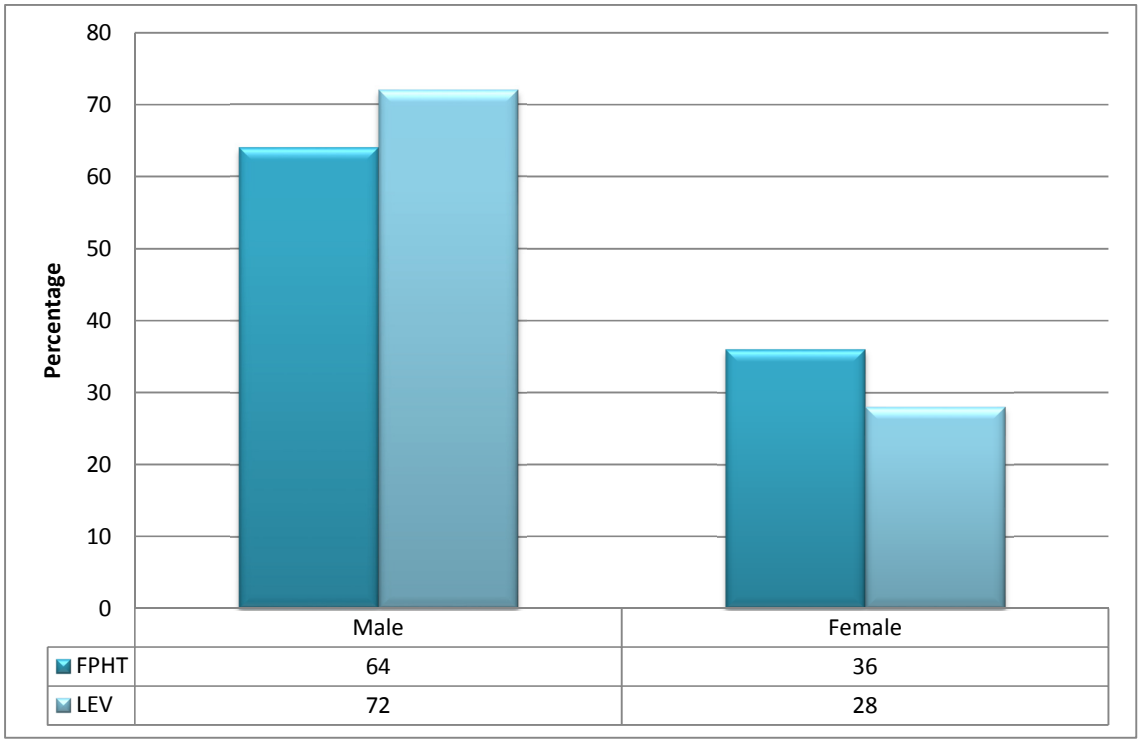
TABLE 10 - COMPARISON OF CASE DISTRIBUTION BASED ON GENDER IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter (sex)	Group I (fosphenytoin) (n=25)	Group II (levetiracetam) (n=25)	'p' value	Statistical Test
1	Male	64%(16)	72%(18)	0.762 (NS)	Fisher's Exact test
2	Female	36%(9)	28%(7)		

Data are expressed as percentages. 'p' value less than 0.05 is considered as significant and Fisher's Exact test was used to test the significance.

- 34 male children (68%) and 16 female children (32%) with Status Epilepticus were enrolled in this study.
- Among the male children, 16 of them were included in Fosphenytoin group and remaining in Levetiracetam group.
- Of the female children, 9 of them received Fosphenytoin and remaining received Levetiracetam.

FIGURE 6 – COMPARISON OF CASE DISTRIBUTION BASED ON GENDER IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



**Data are expressed as absolute numbers.*

**The Length of the bar in vertical bar diagram represents number of subjects (n).*

**The total number of sample in each group is 25.*

3) COMPARISON OF WEIGHT OF THE CHILDREN BETWEEN TWO GROUPS:

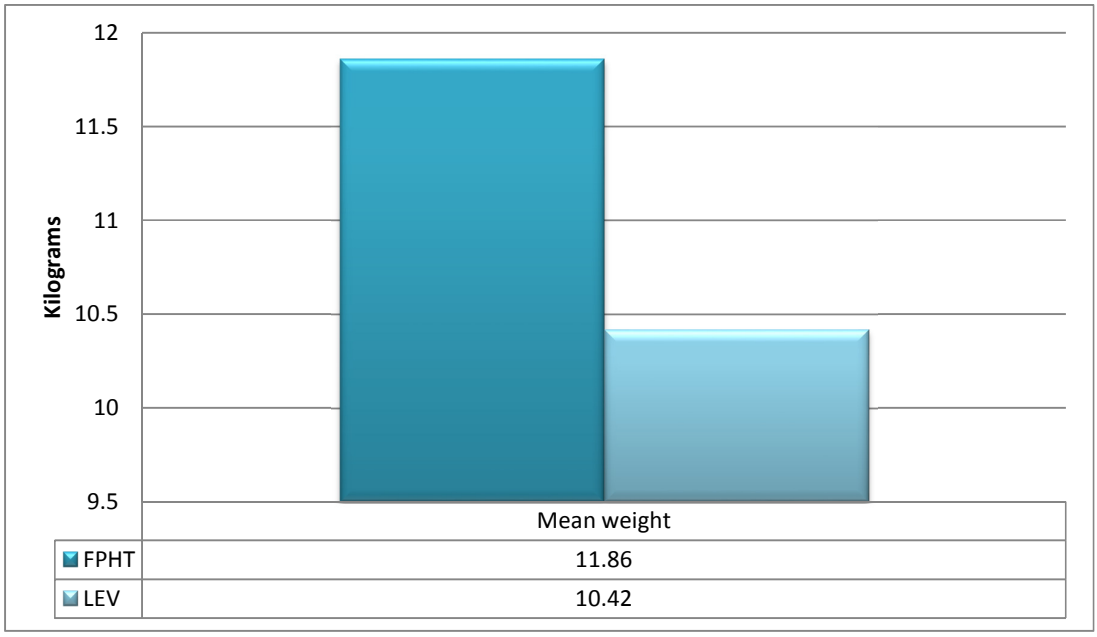
TABLE 11.COMPARISON OF CASE DISTRIBUTION BASED ON WEIGHT IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'P' Value	Statistical Test
1	Weight (in kg)	11.86 ± 8.9	10.42 ± 5.9	0.95 (NS)	Mann-Whitney U test

Data are expressed as mean ±SD. 'p' value less than 0.05 is considered as significant and Mann Whitney U test was used to test the significance.

In this study mean weight of children enrolled in Fosphenytoin group was 11.86 ± 8.9 kg whereas in Levetiracetam group it was 10.42 ± 5.90 kg which was not statistically significant ('p'=0.95)

FIGURE 7 – COMPARISON OF CASE DISTRIBUTION BASED ON WEIGHT IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



**Data are expressed as mean ± SD.*

**The height of the bar in the vertical bar diagram represents the mean.*

**The error bar represents the standard deviation.*

Hence this study is a randomized control using age, gender and weight specific matching.

4) COMPARISON OF DEVELOPMENTAL STATUS:

TABLE 12 - COMPARISON OF CASE DISTRIBUTION BASED ON DEVELOPMENTAL STATUS IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S.no	Parameter Development	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'P' Value	Statistical Test
1	Abnormal	32%(8)	28%(7)	0.999 (NS)	Fisher's Exact test
2	Normal	68%(17)	72%(18)		

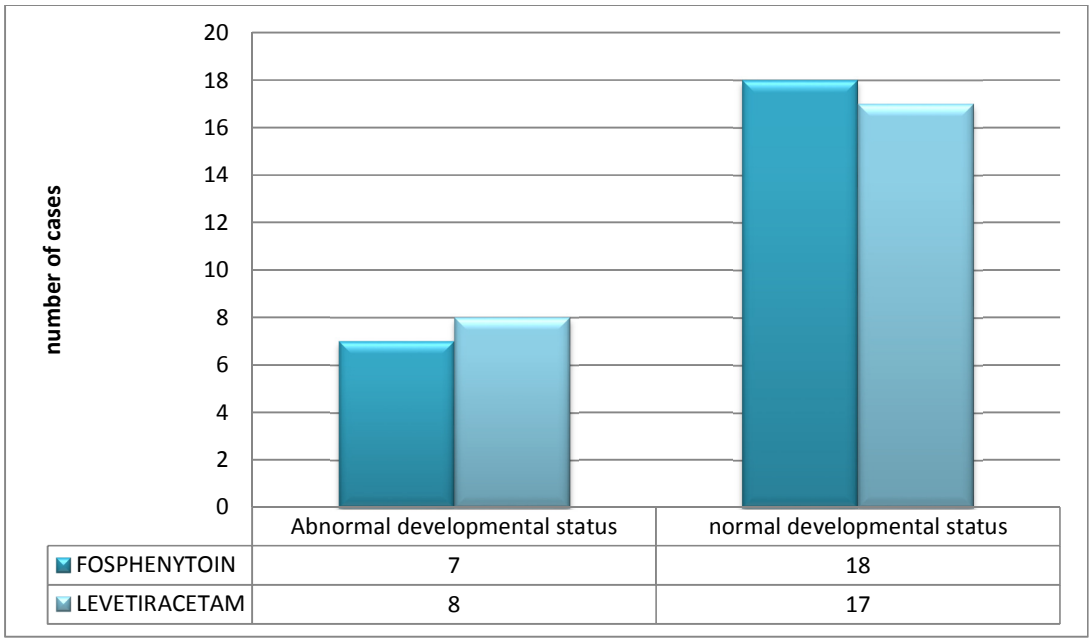
Data are expressed as percentages. 'p' value less than 0.05 is considered as significant and Fisher's Exact test was used to test the significance.

Among the 50 children, 30% (15) of them were developmentally abnormal.

Of whom, eight were treated with Fosphenytoin and seven with Levetiracetam.

However 'P' value was found to be statistically insignificant (0.999).

FIGURE 8 COMPARISON OF CASE DISTRIBUTION BASED ON DEVELOPMENTAL STATUS IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



	Abnormal developmental status	normal developmental status
FOSPHENYTOIN	7	18
LEVETIRACETAM	8	17

**Data are expressed as absolute numbers.*

**The Length of the bar in the vertical bar diagram represents number of subjects (n).*

5) COMPARISON OF PREVIOUS HISTORY OF SEIZURES:

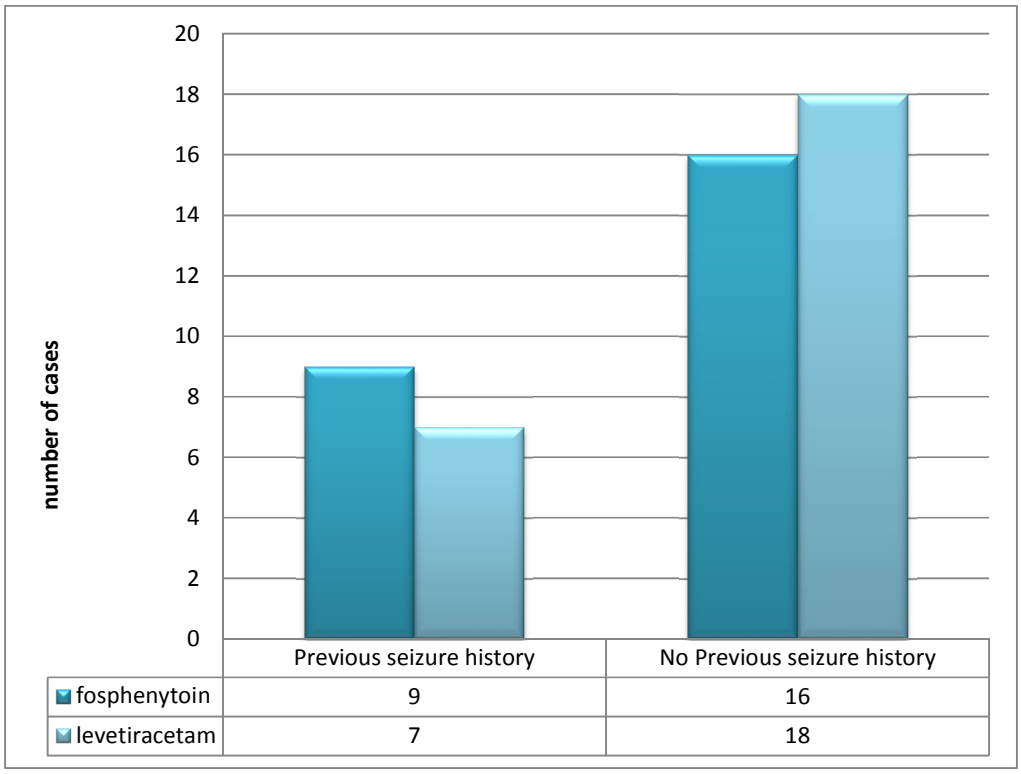
TABLE 13 - COMPARISON OF CASE DISTRIBUTION BASED ON PREVIOUS SEIZURE HISTORY IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter (Previous seizure)	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'P' Value	Statistical Test
1	Yes	36%(9)	28%(7)	0.762 (NS)	Fisher's Exact test
2	No	64%(16)	72%(18)		

Data are expressed as percentage. 'p' value less than 0.05 is considered as significant and Fisher's Exact test was used to test the significance.

Among the 50 children, 16 children had a previous history of seizures. Among those, 9 of them were treated with Fosphenytoin and 7 with Levetiracetam. The 'p' value was not significant.

FIGURE 9 – COMPARISON OF CASE DISTRIBUTION BASED ON PREVIOUS SEIZURE HISTORY IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



**Data are expressed as absolute numbers.*

**The Length of the bar in the vertical bar diagram represents number of subjects (n).*

6) *COMPARISON OF FREQUENCY OF PREVIOUS ANTI-EPILEPTIC DRUG INTAKE IN BOTH GROUPS:*

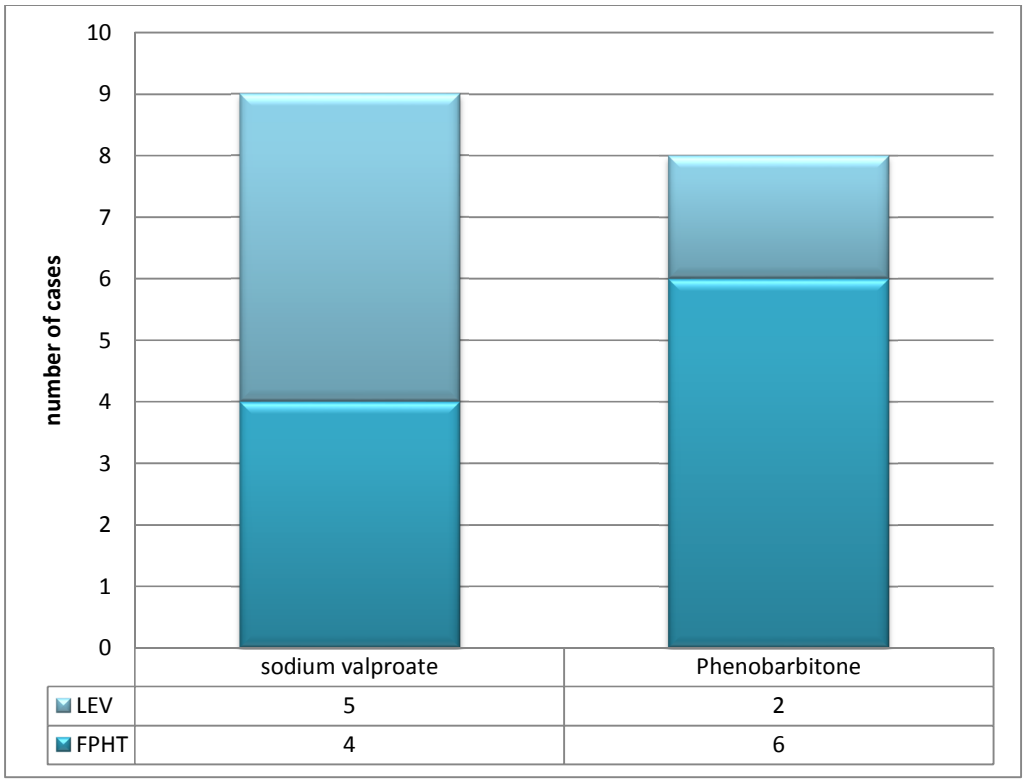
TABLE 14 - COMPARISON OF CASE DISTRIBUTION BASED ON PREVIOUS AED INTAKE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Previous Drug	Fosphenytoin Group (n=25)	Levetiracetam Group (n=25)	Total
1	Sodium valproate	4	5	9
2	Phenobarbitone	6	2	8
3	No drug	15	18	33
	TOTAL	25	25	50

Data is expressed in percentage. 'p' value less than 0.05 is considered as significant and Fisher's Exact test was used to test the significance.

Out of 50 children, 17 of them had previous anti-epileptic drug intake. 10 of them received Fosphenytoin and the remaining 7 children were treated with Levetiracetam (p=0.762 , not significant).

FIGURE 10 - COMPARISON OF CASE DISTRIBUTION BASED ON PREVIOUS AED INTAKE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



7) COMPARISON OF TYPE OF SEIZURES IN BOTH GROUPS:

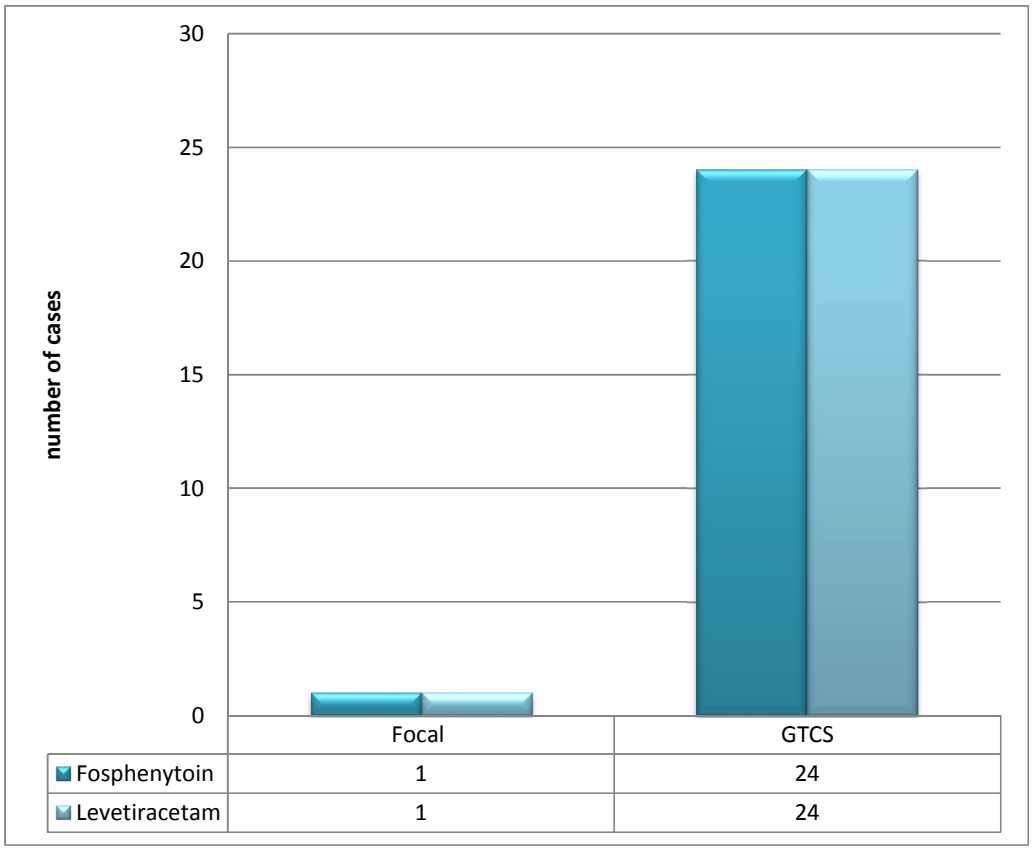
TABLE 15 - COMPARISON OF CASE DISTRIBUTION BASED ON THE TYPE OF SEIZURE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter (type of seizure)	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'P' Value	Statistical Test
1	Focal	4%(1)	4%(1)	0.999 (NS)	Fisher's Exact test
2	Generalised	96%(24)	96%(24)		

Data is expressed in percentage. 'p' value less than 0.05 is considered as significant and Fisher's Exact test was used to test the significance.

Among the 50 children, only 2 children had focal seizures and remaining 48 children had generalized tonic clonic seizures which was not statistically significant ('p'=1.000).

FIGURE 11– COMPARISON OF CASE DISTRIBUTION BASED ON THE TYPE OF SEIZURE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



**Data are expressed as absolute numbers.*

**The Length of the bar in the vertical bar diagram represents number of subjects (n).*

8) COMPARISON OF DURATION OF SEIZURES IN BOTH GROUPS:

TABLE 16 - COMPARISON OF CASE DISTRIBUTION BASED ON THE DURATION OF SEIZURE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

S. No.	Parameter	Group I (Fosphenytoin)	Group II (Levetiracetam)	'P' Value	Statistical TesT
1	Duration of seizure (in minutes)	21.48 ± 4.28	22.12 ± 4.97	0.628 (NS)	Unpaired 't' test

Data is expressed as Mean ± SD. 'p' value less than 0.05 is considered as significant and Mann Whitney U test was used to test the significance.

The mean duration of seizure activity in fosphenytoin group was 21.48 ± 4.28 minutes whereas in levetiracetam group it was 22.12 ± 4.97 minutes which was not statistically significant ('p'=0.628)

FIGURE 12 COMPARISON OF CASE DISTRIBUTION BASED ON THE DURATION OF SEIZURE IN FOSPHENYTOIN AND LEVETIRACETAM GROUP

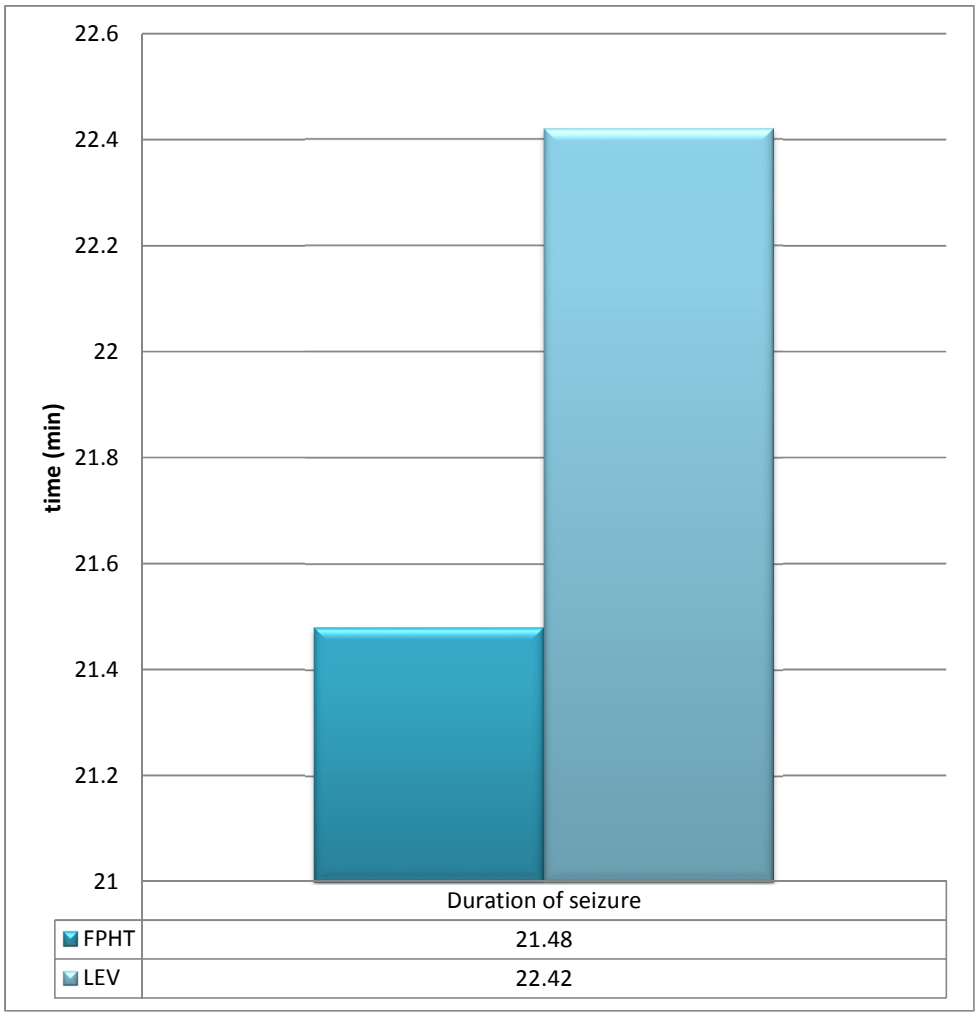
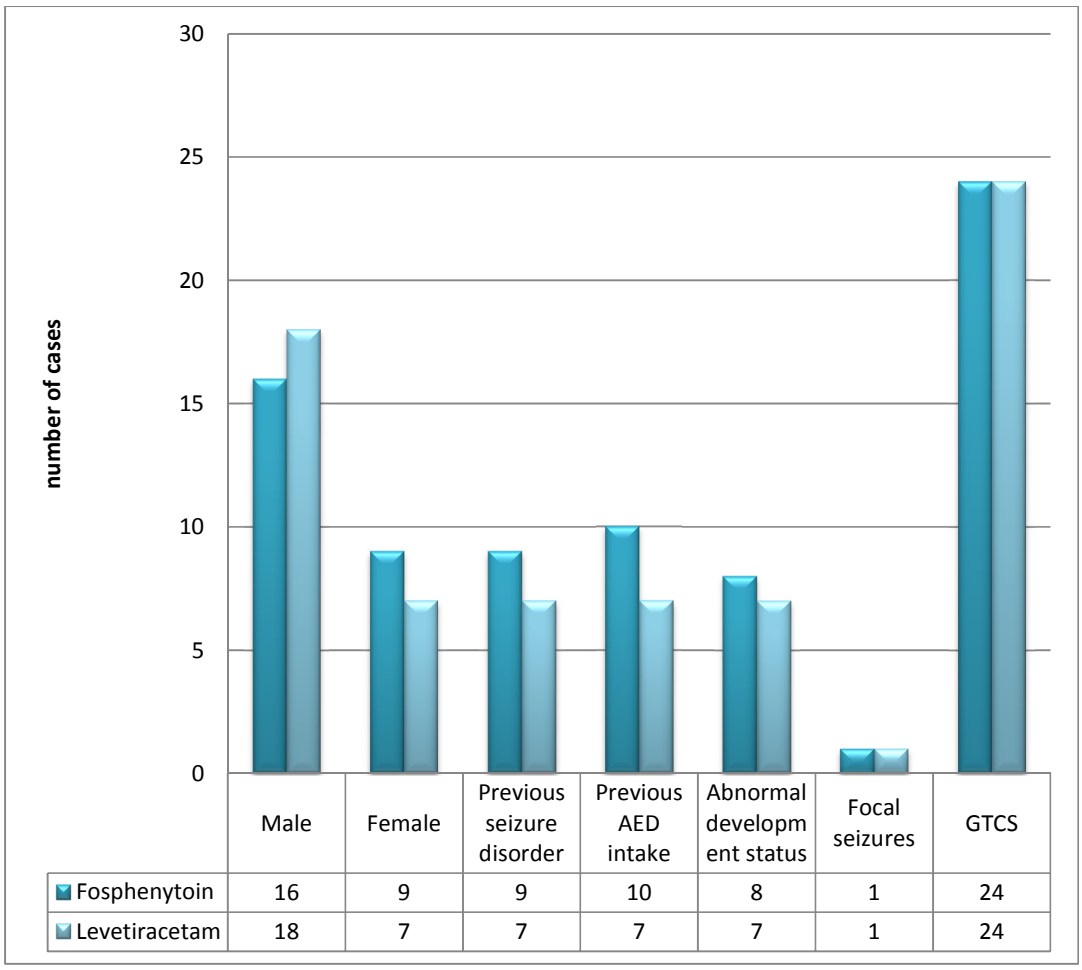


FIGURE 13 COMPARISON OF ALL BASELINE CHARACTERISTICS BETWEEN BOTH STUDY GROUPS:



	Male	Female	Previous seizure disorder	Previous AED intake	Abnormal development status	Focal seizures	GTCS
Fosphenytoin	16	9	9	10	8	1	24
Levetiracetam	18	7	7	7	7	1	24

TABLE 17 - BASELINE CHARACTERISTICS AND THEIR 'P' VALUE

S. No.	Parameter		FPHT Group (n=25)	LEV Group (n=25)	'P' Value	Inference
1	AGE (mean ± SD) in years		3.34 ± 3.6	2.28 ± 2.19	0.657	Not significant
2.	GENDER	Male	16(64%)	18(72%)	0.762	Not significant
		Female	9(36%)	7(28%)		
3.	WEIGHT (in kg)		11.86 ± 8.9	10.42 ± 5.9	0.95	Not significant
4	PREVIOUS SEIZURE DISORDER	Yes	9(36%)	7(28%)	0.762	Not significant
		No	16(64%)	18(72%)		
5	TYPE OF SEIZURE	Focal	1(4%)	1(4%)	0.999	Not significant
		GTCS	24(96%)	24(96%)		
6.	DEVELOPMENT	Abnormal	8(32%)	7(28%)	0.999	Not significant
		Normal	17(68%)	18(72%)		
7.	DURATION OF SEIZURES (minutes)		21.48 ± 4.28	22.12 ± 4.97	0.628	Not significant

TABLE 18 - ETIOLOGICAL PROFILE OF THIS STUDY POPULATION

S.no	ETIOLOGY	FPHT (n=25)	LEV (n=25)
1	Cryptogenic	7(28%)	5(20%)
2	Acute CNS infection	4(16%)	6(24%)
3	Febrile seizures	4(16%)	4(16%)
4	HIE Sequelae	3(12%)	4(16%)
5	Seizure disorder (non-compliance)	3(12%)	1(4%)
6	Syndromic association	1(4%)	1(4%)
7	Hypoglycemia	1(4%)	1(4%)
8	Thulasi oil intoxication	1(4%)	0(0%)
9	Seizure disorder (Breakthrough disorder)	0(0%)	1(4%)
10	Sepsis	1(4%)	0(0%)
11	Camphor intoxication	0(0%)	1(4%)
12	Post meningo-encephalitic sequelae	0(0%)	1(4%)

FIGURE 14 – ETIOLOGICAL PROFILE OF FOSPHENYTOIN GROUP

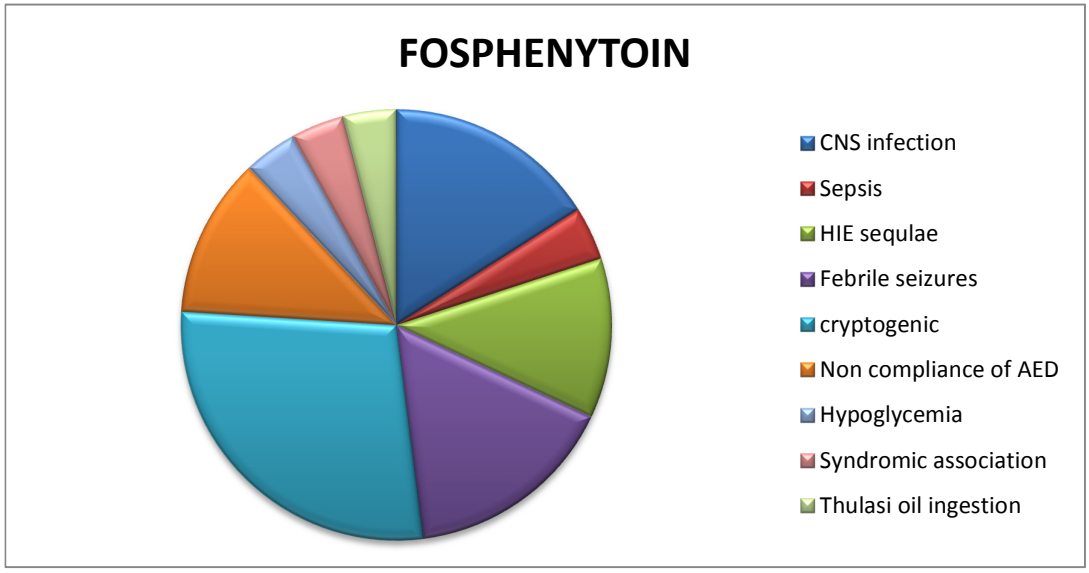
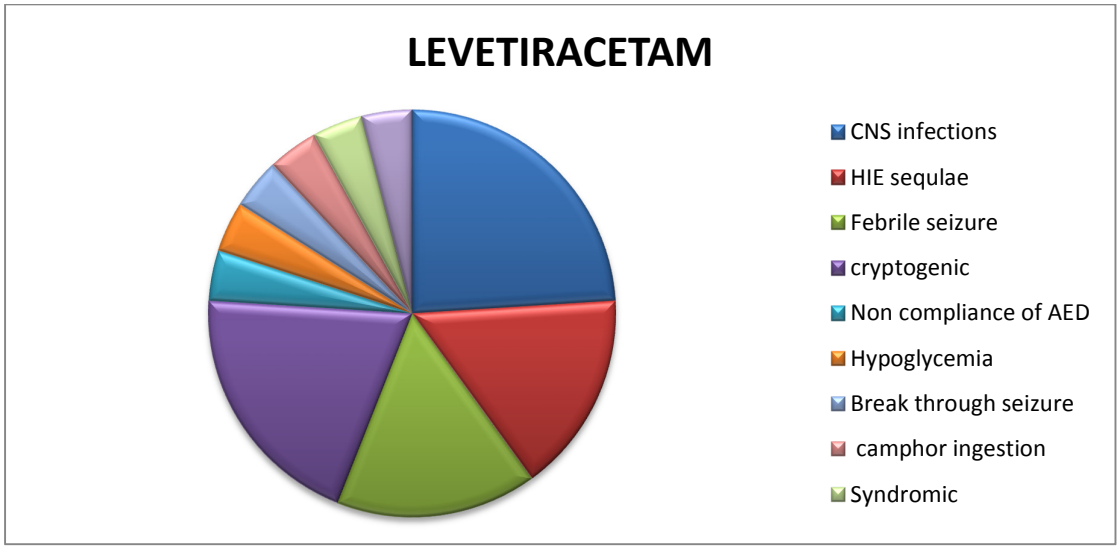


FIGURE 15 – ETIOLOGICAL PROFILE OF LEVETIRACETAM GROUP



STATISTICAL ANALYSIS OF THE OUTCOME OF THE STUDY:

PRIMARY OUTCOME:

A. TERMINATION OF SEIZURE ACTIVITY AFTER DRUG ADMINSTRATION

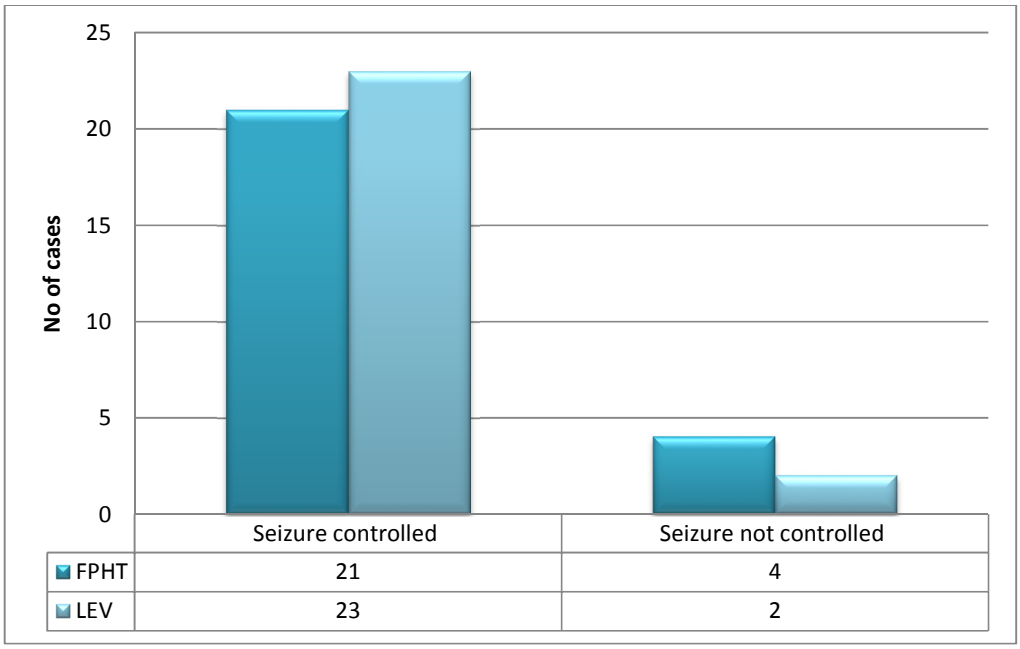
TABLE 19-COMPARISON OF SEIZURE CESSATION RATE FOLLOWING DRUG ADMINISTRATION IN FPHT AND LEV GROUP

S. No.	Parameter (Termination of seizure)	Group I (Fosphenytoin) (n=25)	Group II (Levetiracetam) (n=25)	'P' Value	Statistical Test
1	Yes	84% (21)	92%(23)	0.6671 (NS)	Fisher's Exact test
2	No	16%(4)	8%(2)		

In our study, seizure cessation rate following fosphenytoin administration was 84% whereas for levetiracetam it was 92%. However 'p' value was found to be insignificant.

The percentage of children requiring additional anti-epileptic drugs to terminate the presenting convulsions was 16% and 8% for fosphenytoin and levetiracetam group respectively.

FIGURE 16-COMPARISON OF SEIZURE CESSATION RATE FOLLOWING DRUG ADMINISTRATION IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



B. *TIME TAKEN TO TERMINATE SEIZURES:*

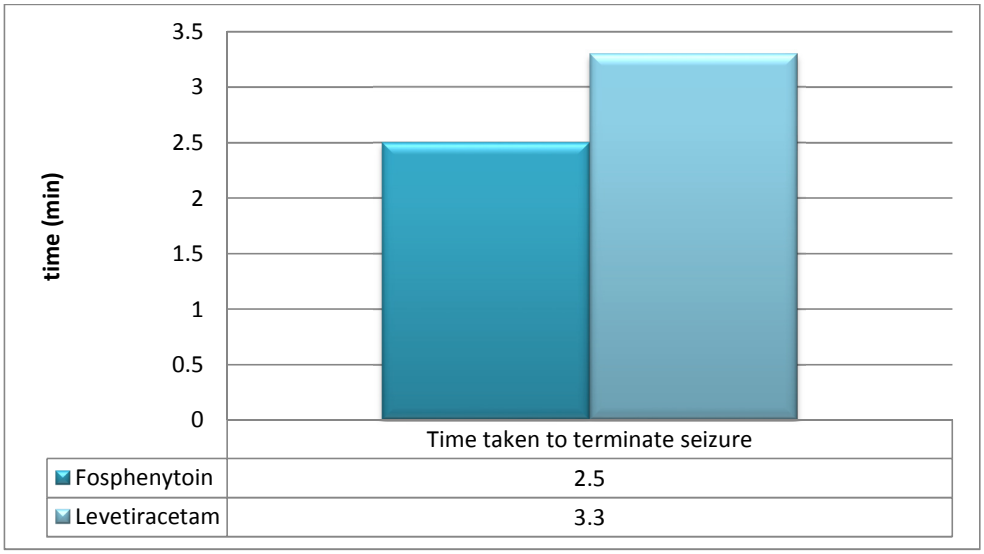
TABLE 20– COMPARISON OF TIME TAKEN TO TERMINATE SEIZURES FOLLOWING DRUG ADMINISTRATION IN FPHT AND LEV GROUP

S. NO.	Parameter	Fosphenytoin Group	Levetiracetam Group	'P' Value	Statistical Test
1	Time needed to terminate seizure	2.5 ± 1.4 min	3.3 ± 1.16 min	0.029*	Unpaired 't' test

In our study the mean time taken to terminate seizures was 2.5 ± 1.4 minutes in Fosphenytoin group. For Levetiracetam it was about 3.3 ± 1.16 minutes.

The 'P' value was found to be statistically significant (0.029)

FIGURE 17-COMPARISON OF TIME TAKEN TO TERMINATE SEIZURES FOLLOWING DRUG ADMINISTRATION IN FOSPHENYTOIN AND LEVETIRACETAM GROUP



SECONDARY OUTCOMES:

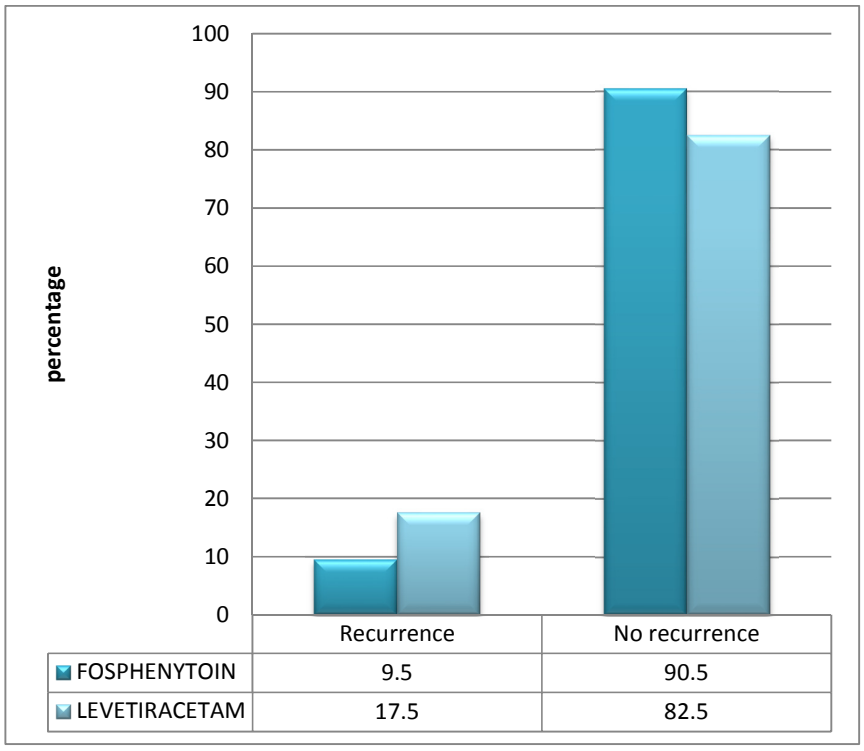
*C.**RECURRENCE OF SEIZURE:***

TABLE 21-COMPARISON OF RECURRENCE OF SEIZURE IN FPHT AND LEV GROUP

S. No.	Parameter (Recurrence)	Fosphenytoin Group (n=21)	Levetiracetam Group (n=23)	'P' Value	Statistical Test
1	Yes	9.5%(2)	17.5%(4)	0.44	Fisher's Exact Test
2	No	90.5%(19)	82.5%(19)		
3	Total	21	23		

In our study, Fosphenytoin group had a recurrence of 9.5% whereas levetiracetam group had 17.5% recurrence. The 'P' value was found to be insignificant. Hence both fosphenytoin and levetiracetam had no significant variations in causing breakthrough seizures.

FIGURE 18-COMPARISON OF RECURRENCE OF SEIZURE IN FPHT AND LEV GROUP.



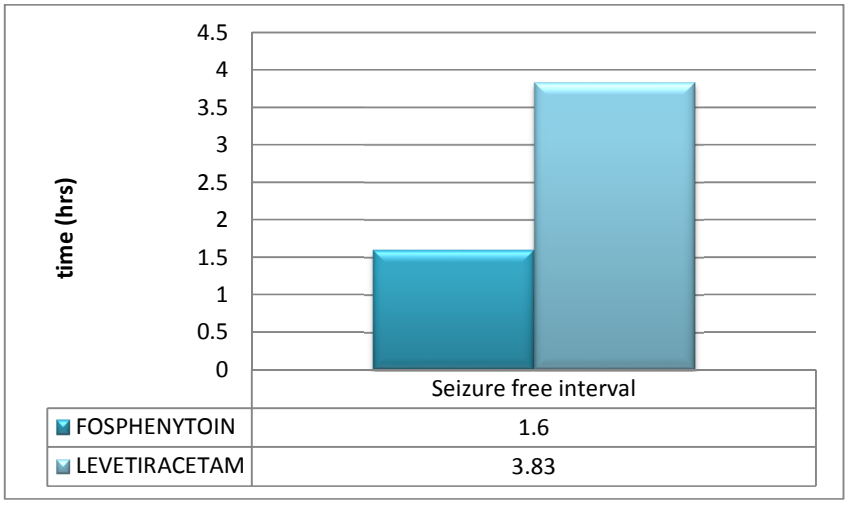
*D.**SEIZURE FREE INTERVAL:***

TABLE 22 - COMPARISON OF SEIZURE FREE DURATION FOLLOWING DRUG ADMINISTRATION IN FPHT AND LEV GROUP WHEN SEIZURE RECURS

S. No.	Parameter	Fosphenytoin Group(n=2)	Levetiracetam Group(n=4)	'P' Value	Statistical test
1.	Seizure free interval (hours)	1.6±1.1	3.8±6.3	0.8	Mann Whitney U test

In our study, there was no significant variation in seizure free duration following drug administration between both groups

FIGURE 19 - COMPARISON OF SEIZURE FREE DURATION FOLLOWING DRUG ADMINISTRATION IN FPHT AND LEV GROUP WHEN SEIZURE RECURS



E.IMPACT ON HOSPITAL STAY:

TABLE 23- COMPARISON OF LENGTH OF PICU AND HOSPITAL STAY IN FPHT AND LEV GROUP

S. No.	Duration of stay	Fosphenytoin Group	Levetiracetam Group	'P' Value	Statistical test
1	PICU(hours)	42.3 ± 65.1	44 ± 26.7	0.105	Mann Whitney U test
2	Hospital(days)	5.8 ± 4.9	6.3± 3.7	0.311	

There was no difference in the length of PICU (42.3 hours vs. 44 hours) and hospital stay between two groups. The mean duration of hospital stay for Fosphenytoin group was 6.41 days and for Levetiracetam group was 6.06 days.

FIGURE 20- COMPARISON OF LENGTH OF PICU STAY IN FPHT AND LEV GROUP

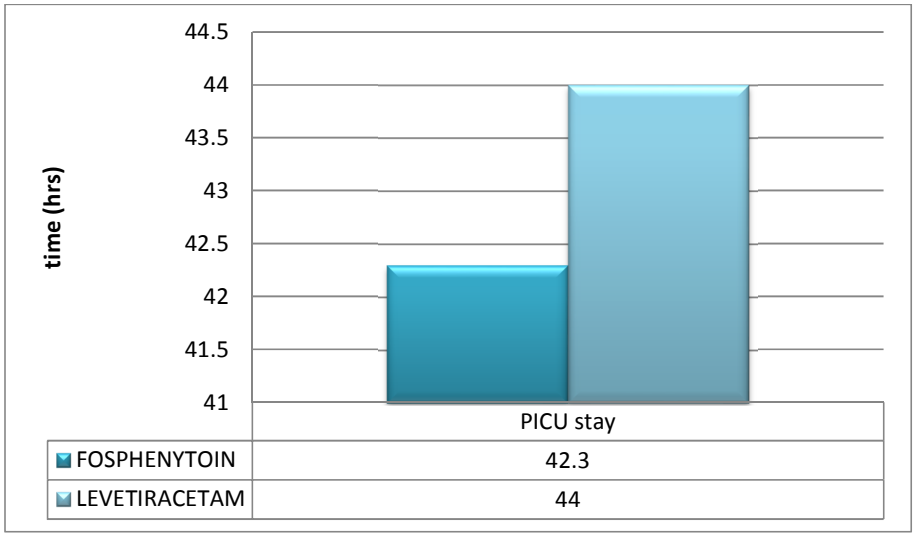


FIGURE 21- COMPARISON OF LENGTH OF HOSPITAL STAY IN FPHT AND LEV GROUP

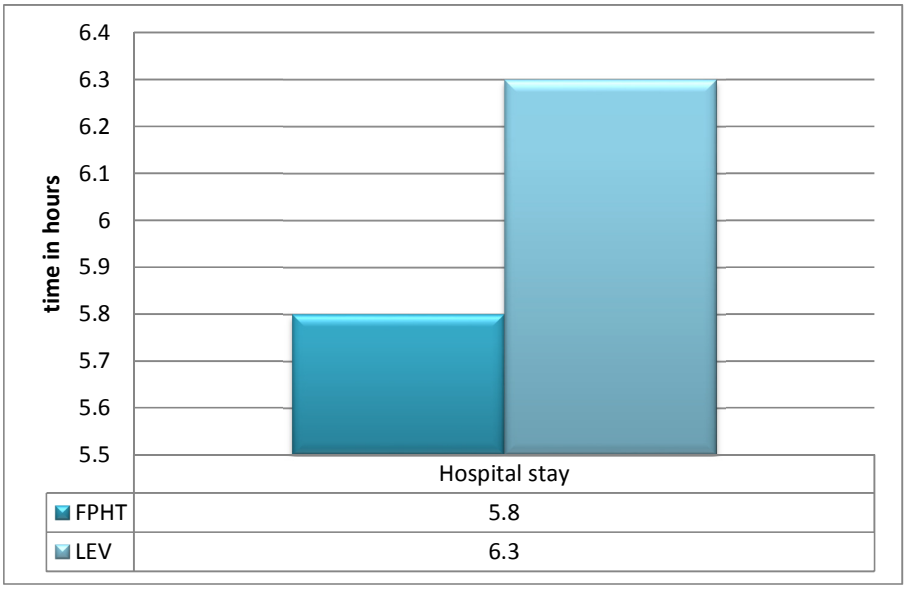
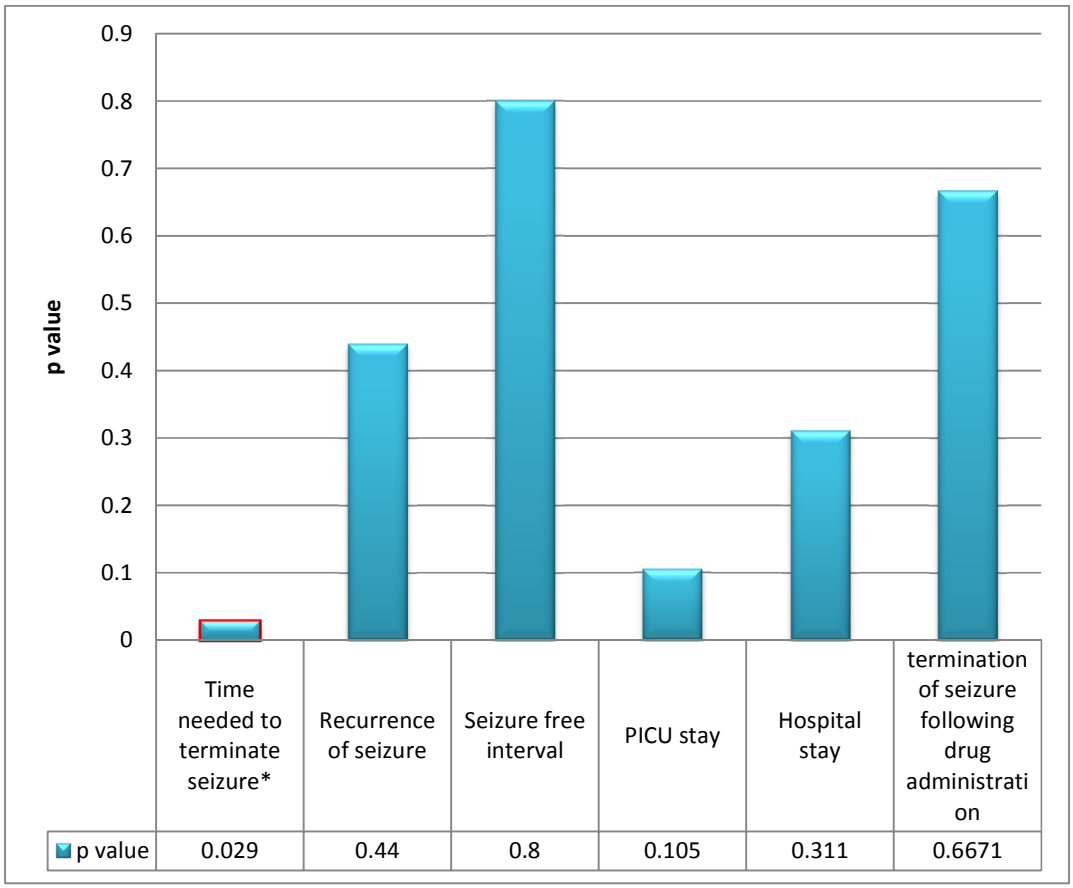


FIGURE 22- COMPARISON OF 'P' VALUES OF BOTH PRIMARY AND SECONDARY OUTCOMES BETWEEN FOSPHENYTOIN AND LEVETIRACETAM GROUP



*Statistically significant.

E. NEED FOR VENTILATORY ASSISTANCE AND LIFE THREATENING HYPOTENSION*:*

TABLE 24 – COMPARISON OF LIFE THREATENING ADVERSE DRUG REACTIONS IN FPHT AND LEV GROUP

S.no	Adverse event observed	FPHT Group	LEV Group	
1	Hypotension treated with inotropes	1(4%)	1(4%)	These adverse effects were documented in children who needed additional AEDs to terminate the presenting seizures.
2	Respiratory depression (ventilator assistance)	4(16%)	1(4%)	

***F.ADVERSE EFFECTS**:*

TABLE 25 – COMPARISON OF SPECIFIC ADVERSE DRUG REACTIONS IN FPHT AND LEV GROUP WHO DID NOT REQUIRE ADDITIONAL AEDS

S. No.	ADVERSE EFFECT	FOSPHENYTOIN	LEVETIRACETAM
1	Respiratory depression (non-intubated)	1(4%)	0(0%)
2	Ataxia	1(4%)	0(0%)
3	Behavioral changes (irritable cry & somnolence)	0(0%)	1(4%)
4	Thrombocytopenia	0(0%)	1(4%)

TABLE 26 - DEPICTS THE COMPARISON OF EFFICACY OF BOTH DRUGS

S. No.	Parameter	Fospheytoin Group	Levetiracetam Group	'P' Value	Inference
1	Seizure termination rate	84%	92%	0.6671	Not significant
1.	Time taken to terminate seizures (minutes)	2.5±1.4	3.3 ± 1.16	0.029*	Significant
2.	Recurrence of seizures	9.5%	17.5%	0.44	Not significant
3.	Seizure free interval (hours)	1.6 ± 1.1	3.8 ± 6.3	0.8	Not significant
4.	PICU stay (hours)	42.3± 65.1	44 ± 26.7	0.105	Not Significant
5.	Hospital stay (days)	5.8 ± 4.9	6.3± 3.7	0.311	Not significant
6.	Adverse events	8%	8%	-	-

In our study Fosphenytoin terminated seizures in 84% of the children whereas levetiracetam's seizure cessation rate was 92%. Fosphenytoin terminated seizure earlier than Levetiracetam (2.5 minutes vs. 3.3 minutes; P= 0.029*).

Comparison of efficacy of Fosphenytoin and Levetiracetam in different domains including recurrence of seizures, seizure free duration and hospital stay were not statistically significant.

On comparing the secondary outcome following treatment with either fosphenytoin or levetiracetam; 2 cases had adverse drug reactions in each group. One child had respiratory depression requiring nasal oxygen and other developed transient ataxia following fosphenytoin infusion. In levetiracetam group behavioral changes and thrombocytopenia were the adverse events noted.

Case fatality rate was 8% in our study. All the children required additional AED & the cause of death was mutifactorial

TABLE 27 – MORTALITY AND ITS ASSOCIATIONS IN THIS STUDY

S.no	PREDICTORS	NUMBER OF CASES (n=4)		
		FPHT	LEV	TOTAL (n=4)
1	Age less than 1 year	3	1	4
2	Need of additional AEDs to terminate seizures	3	1	4
3	Acute symptomatic etiology	2	1	3
	Remote symptomatic etiology	1	0	1
4	Focal seizures	0	1	1
	Generalize Tonic clonic seizures	3	0	3

DISCUSSION

The study was done during a period of 6 months from January -June 2017. There were a total of 68 children who presented with status epilepticus during this time period of which, 50 children fulfilled the inclusion criteria. Among those 50 children, 25 of them were treated with Fosphenytoin and the remaining with Levetiracetam.

In this study, we compared fosphenytoin with levetiracetam in terms of their effectiveness (both efficacy and adverse drug reactions) in benzodiazepine resistant status epilepticus.

In the study Group I (Fosphenytoin group), 64% were male children. The mean age was 3.34 years; with a mean weight of 11.86 kg and mean seizure duration of 21.48 minutes. Previous AED intake was found in 10 cases and delayed developmental milestones in 32%.

In the study Group II (Levetiracetam group), 72% were male children. The mean age was 2.28 years; with a mean weight of 10.42 kg and mean seizure duration of 22.12 minutes. Previous AED intake was found in 7 cases and delayed developmental milestones in 28%.

The most common type of seizure was GTCS followed by focal seizures in 8%. None had myoclonic seizures.

The etiology of seizures in the study group with decreasing order of frequency based on clinical findings were acute symptomatic (acute CNS infection, hypoglycemia and intoxication), remote symptomatic , cryptogenic status epilepticus and febrile status epilepticus.

In our study, seizure cessation rate following fosphenytoin administration was 84% whereas for levetiracetam it was 92%. In a previous study done by Zeid Yasiry et al, the efficacy of levetiracetam was 68.5% and phenytoin was 50.2%. [32] In their study, 798 cases of convulsive SE were analyzed retrospectively. The study by Alvarez et al throws a contrary picture with seizure cessation rate of 58.2% and 51.7% for phenytoin and levetiracetam respectively, which was statistically insignificant as in our study. [27] There is no previous data comparing fosphenytoin with levetiracetam in children.

TABLE 28 - COMPARISON OF VARIOUS STUDIES WITH REGARDING TO SEIZURE CESSATION RATE

S. No.	Study	Phenytoin /Fosphenytoin	Levetiracetam	'P' Value
1	Our study	84% (fosphenytoin)	92%	Not significant
2	Zeid Yasiry et al	50.2% (phenytoin)	68.5%	-
3	Alvarez et al	58.2% (phenytoin)	51.7%	Not significant

In our study fosphenytoin terminated seizures earlier than levetiracetam. The mean time taken to terminate seizures was 2.5 ± 1.4 minutes in fosphenytoin group. For levetiracetam it was about 3.3 ± 1.16 minutes. According to Jaclyn O'Connor and her associates, time needed to terminate seizures was similar (P= 0.085) in both study groups. [3] However their study was done on adults.

In the fosphenytoin group, 9.5% (2/21) had recurrence, whereas the levetiracetam group had 17.5% (4/23) recurrence which is similar to the results of a study in adults done by Chakravarthy et al. [28] It is not comparable to the study done by Jacyln O' Connor and her colleagues, where breakthrough seizures occurred less in LEV group (22%vs.38% p=0.014*.)[3]

In our study, there was no significant variation in seizure free duration following drug administration between both groups. None of the studies compared this parameter.

There was no difference between the two groups in length of PICU (42.3 vs. 44; p= 0.105) and hospital Stay (5.8 days hrs vs. 6.3 days; p= 0.311). This was similar to the study conducted by Jaclyn O' Connor et al between these two drugs on adults. [3]

In a systematic review by Egunsola O et al on the safety of levetiracetam in pediatric population, it was found that behavioral problems and somnolence to be the most prevalent adverse event to levetiracetam. [21]

In our study, behavioral changes were observed in 4% of cases in the form of irritable cry.

According to Kinshuk Sahaya, out of 755 patients, 29 patients were recognized with fall in platelet count while on levetiracetam prophylaxis. [34] In our study, only one child (4%) was documented to have thrombocytopenia. The cause of thrombocytopenia is uncertain in view of associated sepsis in that child.

In a study by Jamerson et al, 8 out of 12 patients treated with phenytoin experienced phlebitis but was noted on only one case with fosphenytoin ($P < 0.05$)[35]. In our study, no case of phlebitis was documented.

According to Leppik and his colleagues, serious cardiovascular and respiratory adverse reactions were not observed during IV infusion of FPHT [33]. In our study, hypotension was noted in two cases (1 each from FPHT & LEV group), but they also needed additional AEDs (like phenobarbital or midazolam) to terminate the seizures.

In Ramsay RE and Wilder BJ et al study, 67% of patient receiving parenteral phenytoin experienced transient CNS side effects like nystagmus, ataxia and dizziness but no patient developed intolerance to fosphenytoin. [36] In our study, ataxia was noted in 1 child (4%) treated with fosphenytoin, who recovered on switching to oral anti-epileptic drugs.

LIMITATIONS OF THIS STUDY

- The sample size of the study was small.
- The primary outcome does not include electroencephalography confirmation of seizure termination.
- The cause of death was multifactorial.

SUMMARY

50 children aged between 1 month and 12 years presenting to pediatric emergency department at Govt. Rajah Mirasdar hospital, Thanjavur from January 2017 to June 2017 with status epilepticus that has failed to terminate with two doses of midazolam were included in this study. Children in shock, who were on oral phenytoin and levetiracetam medications and who were treated with injectable antiepileptic drugs in previous 24 hours were excluded from this study.

Participants were administered 30 mg PE/kg of intravenous fosphenytoin over 10 min & 30 mg/kg of intravenous levetiracetam over 6 min. The primary outcome of the study is the clinical cessation of seizure activity and the need for additional AED to terminate seizures. Secondary outcomes includes a) recurrence, b) serious adverse events & c) length of PICU and hospital stay.

Fosphenytoin achieved control of SE in 89% patients compared to levetiracetam in 82% (p=0.6671). Fosphenytoin terminated seizure earlier than Levetiracetam (2.54mins vs. 3.3 mins; P=0.029). There was no significant difference between the two groups with respect to recurrence of seizures within 24 hours (p=0.44), seizure free duration when seizure recurs (p=0.8) and duration of PICU and hospital stay (p=0.105 & 0.311) .The adverse events did not differ significantly between two groups.

CONCLUSION

Fosphenytoin terminated seizures earlier than levetiracetam. Levetiracetam may be an effective alternative to fosphenytoin in management of SE in children in view of comparable efficacy in terms of termination of seizures, recurrence of seizures, adverse events & length of hospital stay.

ANNEXURE 1

BIBLOGRAPHY

1) Mishra D et al. Consensus guidelines on management of childhood convulsive status epilepticus. Indian Pediatr 2014Dec;51(12):975-90.
2) Delorenzo RJ, Pellock JM, Towne AR, Boggs JG. Epidemiology of status epilepticus. J clin neurophysiol. 1995Jul;12(4): 316-25.
3) Jaclyn OC, Philip L, Wilson, Saely S. Levetiracetam is as effective as phenytoin in status epilepticus with less adverse events in the ED. Critical care medicine. 2015Dec; 43(12):6.doi:10. 1097/01.ccm. 0000473848.40708.ea.
4) Kliegman, Stanton, st Geme, Schor – Nelson text book of paediatrics. 20 Edition.Philadelpia, Elsevier. Vol 3: Page no 2823-57
5) Roger J, Lob H , Tassinari CA , status epilepticus , In magnus O de Lerentz Haas AM (Ed) Handbook of clinical neurology vol 15 .the epilepsies . Amsterdam : North Holland publishing company , 1974: 145-188.
6) Trinka E et al. A Definition and classification of status epilepticus – report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015Oct;56(10):1515-23.doi:10.1111/epi. 13121

7) Sanchez S and Rincon F. Status Epilepticus: epidemiology & public needs. J Clin Med.2016Aug;5(18):71.doi:10.3390/jcm5080071.

8) Dixit AB, Bannerjee J, Chandra PS, Tripathi M. Recent advances in epilepsy research in India. Epilepsia. 2017;65(7):83-92.doi:10.4103/ neuroindia NI -1070-16.

9) Chin RF, Nevilli BG, Peckham C, Bedford H, Wade A and Scott AC. Incidence, cause and short term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006Jul;368(9531):222-9.doi:10.1016/50140-6736(06)69043-0.

10) Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus. Frequency, risk factors and impact on outcome. Arch Neurol. 2002Feb;59(2):205-10.doi:10.1001/ archneuro.59. 2.205.

11) Wasterlain CG and Chen JWY. Mechanistic and pharmacological aspects of status epilepticus and its treatment with new antiepileptic drugs. Epilepsia 2008Dec;49(9):63-73.doi:10.1111/j.1528-1167 .2008 .01928.x.

12) Pellock JM, Delorenzo RJ, Towne AR, Ko D. Status Epilepticus in children, adults and the elderly. Epilepsia. 1992Jul;33(4):15-25.doi:10.1111/j.1528.1157.1992.6606223.x.

13) Nelgian A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus; A review. Epilepsy Res.2011Jan; 93(1):1-10. doi:10.1016/j.eplepsyres 2010.09.003. Epub 2010 act 13.

14) Raspall Chaure M, Chin R.F, Neville B.G, Scott R.C- Outcome of pediatric convulsive status epilepticus –A systematic review. Lancet neurol. 2006Sep;5(9):769-79.doi:10.1016/s1474-4422(06)70546-4.

15) Maytal J, Shinnar S, Moshi SL, Alvarez LA. Low morbidity and mortality of Status epilepticus in children. Pediatrics 1989Mar;83(3):323-31.

16) Gabor AJ, Brooks AG, Scobey RP, Parson GH. Intracranial pressure during epileptic seizures. Electroencephalogr clin neurophysiol .1984Jun;57(6):497-506.

17) Bleck TP. Intensive care unit management of patients with status epilepticus. Epilepsia.2007;48(8):59-60. doi 10.1111/j.1528-1167.2007.01352.x

18) Fountain NB. Status epilepticus: Risk factors and complications. Epilepsia.2000;41(2):23-30.

19) Pacifici GM. Clinical pharmacology of midazolam in neonates and children : Effect of disease – A review. Int J Pediatr. 2014Feb;309342.doi /10.115/2014/309342

20) Stockis A, Tonner F, Lu S, Otoul C. Clinical pharmacology of levetiracetam for treatment of epilepsy. Expert Rev clin pharmacol.2009Jul;2(4);339-50.doi:10.1586/ecp.09.16.

21) Egunsola O, Choonara I and Sammons HM. Safety of Levetiracetam in Pediatrics- A Systematic review PLoS ONE. 2016Mar11(3); e1049686.doi:10.1371/journal.pone 0149686.

22) Wright C. Clinical pharmacology and pharmacokinetics of levetiracetam. 2013Dec;doi10.3389/fneur.2013.00192

23) Tripathi KD(2013) – Essentials of medical pharmacology – Seventh edition- New Delhi, Jaypee Brothers. Chap 30:413-5

24) Hennig S, Norris R, Tu Q, Van Breda K, Foster K. Pharmacokinetics of phenytoin in critically ill children. J chin pharmacol.2015 Mar;55(3);355-64.doi:10.1002/jcph.417.

25). Ogutu BR et al. Pharmacokinetics and clinical effects of phenytoin and Fosphenytoin in children with severe malaria and status epilepticus. Br J clin Pharmacol.2003Jul; 56(1)112-9.

26) Nakamura K et al. Efficacy of levetiracetam versus phenytoin for recurrence of seizure after status epilepticus. Medicine. 2017Jun;96(25):e7206. Doi:10.1097/MD.0000000000007206

27) Alvarez V, Januel JM, Burnand B, Rosetti AO. Second line status epilepticus treatment ; Comparison of phenytoin , valproate and levetiracetam. Epilepsia . 2011Apr;52(7):1292-6. doi:10.1111/j.1528-1167.2011.03056.x

28) Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus Phenytoin in management of status epilepticus. J Clin Neurosci. 2015Jun;22(6):959-63.doi: 10.1016/j.jocn.2014.12.013.

29) Tripathi M. Management of refractory status epilepticus at a tertiary care centre in a developing country. Seizure.2010Mar;19(2):109-11.doi : 10.1016/ seizure 2009.11.007

30) Knake S et al. Intravenous Levetiracetam in thenTreatment of Benzodiazepine Refractory Status Epilepticus. J.neurol neurosurg psychiatry. 2008May;79(5):588-9.

31) Lee T et al. Levetiracetam in toxic seizures. Clin Toxicol(Phila). 2012Jul;28:1-7.doi:10/080/15563650.2017.1355056

32) Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptics in treatment of benzodiazepine resistant convulsive status epilepticus : A meta – analysis of published studies. Seizure.2014Mar;23(3):167-74.doi:10.1016/j.seizure2013.12.007

33) Leppik IE et al. Phenytoin prodrug: preclinical and clinical studies. Epilepsia. 1989Jun;30(2):22-6. doi10.1111/j.1528-1157

34) Sahaya K, Goyal MK, Sarwal A & Singh NA. Levetiracetam – induced thrombocytopenia among inpatients : A retrospective Study .Epilepsia 2010Nov; 51(12) :2492-95.doi:10.1111/j.1528-1167.2010.02788.x

35) Jamerson BD, Dukes GE, Brouwer K L.R, Dorm KH, Messenheimer JA, Powell JR. Venous Irritation Related to Intravenous Administration of Phenytoin versus Fosphenytoin. Pharmacotherapy: The Journal of Human Pharmacotherapy and Drug Therapy.1994Jan;14(1):47-52.doi10.1002/j.1875-9114.1994.tb02788.x

36) Ramsay RE. Intramuscular Fosphenytoin in patients requiring loading dose of phenytoin. Epilepsy Res. 1997Oct;28(3);181-7.

ANNEXURE 2

PROFORMA

NAME - AGE - SEX-

IP NO –

SOCIOECONOMIC STATUS: (modified Kuppusamy scale)

PRESENTING ILLNESS:

Seizure (duration, type, features)

H/O fever

H/O trauma

Other relevant history

PAST ILLNESS:

Whether a known case of seizure disorder or not?

Any AED intake –

TREATMENT HISTORY:

For the presenting complaints, whether the child had been treated outside with any forms of injectable drugs.

FAMILY HISTORY:

Pedigree & Consanguinity:

ANTENATAL/ NATAL/POSTNATAL HISTORY:

(Relevant details)

IMMUNIZATION HISTORY:

DEVELOPMENTAL HISTORY

Gross motor/ Fine motor	Cognition	Social	Activities of daily living

Delay in developmental milestones	
No delay in developmental milestones	

WEIGHT FOR AGE

Normal	>80%	
Grade I malnutrition	70 – 80%	
Grade II malnutrition	60 – 70%	
Grade III malnutrition	50 - 60%	
Grade IV malnutrition	< 50%	

2.HEIGHT

90 %		
90 -95%		
85 -90%		
< 85%		

3. HEAD CIRCUMFERENCE

-3SD TO -2SD	-2 SD TO -1 SD	-1SD TO MEDIAN	MEDIAN TO +1 SD	+ 1 SD TO +2 SD	+ 2 SD TO +3 SD

GENERAL EXAMINATION:

Look for dysmorphism&Look for neurocutaneous marker

VITALS: *1.*HEART RATE:

Bradycardia	
Normal	
Tachycardia	

(Using age specific Heart rate data)

2.RESPIRATORY RATE:

Bradypnoea	
Normal	
Tachypnoea	

(Using age specific respiratory rate data)

3. BLOOD PRESSURE: (Expressed in centile)

Less than 5th centile	
Normal	
More than 95th centile	

4.CAPILLARY REFILL TIME:

Normal	
Prolonged	

5.PERIPHERAL PULSES:

Not felt	
Well felt	

6.TEMPERATURE:

Febrile	
Afebrile	

SYSTEMIC EXAMINATION:

CNS

HIGHER MENTAL FUNCTION:

CRANIAL NERVES:

MOTOR: - Co-ordination

-BULK - TONE - POWER - REFLEXES

PLANTAR REFLEX:

INVOLUNTARY MOVEMENTS:

SENSORY:

CEREBELLAR

S/O MENINGEAL IRRITATION:

CVS

RS

ABDOMEN

DATA ANALYSIS

	FOSPHENYTOIN	LEVETIRACETAM
AVAILABILITY		
COST		

	FOSPHENYTOIN		LEVETIRACETAM	
	PREVIOUSLY NEUROLOGICALLY NORMAL	**PREVIOUSLY NEUROLOGICALLY ABNORMAL**	**PREVIOUSLY NEUROLOGICALLY NORMAL**	**PREVIOUSLY NEUROLOGICALLY ABNORMAL**
ANY PRE-HOSPITAL TREATMENT				
WHETHER STATUS TERMINATED				
TOTAL DURATION NEEDED TO CONTROL STATUS (from drug administered to seizure activity termination)				
RECURRENCE WITHIN 24 hrs				
SEIZURE				

FREE INTERVAL AFTER INITIAL DOSE (in case of recurrence)				
NEED OF ADDITIONAL AED				

CESSATION OF STATUS :

It is the termination of all seizure activity within 30 minutes following drug administration.

ABSENCE OF RECURRENCE :

It is absence of recurrence of seizure within 24 hours

	FOSPHENYTOIN	LEVETIRACETAM
INCIDENCE OF ADR		
DURATION OF PICU STAY		
IMPACT IN HOSPITAL STAY		

FOSPHENYTOIN	**% observed**	**LEVETIRACETAM**	**% observed**
Respiratory depression		Somnolence	
Hypotension		Behaviour changes	
Cardiac arrythmias		ANY OTHERS	
Extravastion of drug when administered through IV			
Did side effects warrant discontinuation of therapy?			
ANY OTHERS			

INVESTIGATIONS:

CBC

RBS

SERUM ELECTROLYTES

SERUM CALCIUM

LFT

DIAGNOSIS:

Seizure type →

Etiology →

Syndromic association →

Etiology	IV Fosphenytoin	IV Levetiracetam
Non – compliance		
Acute CNS infection		
Febrile status		
Metabolic cause		
Miscellaneous		

ANNXEURE 3

CONSENT FORM

I hereby give consent for my child to participate in the study conducted by Dr.KOWSIK.M, post graduate in Department of Pediatrics , Thanjavur Medical College , Thanjavur – 613001 and to use my child's personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease.

Name of the participant-

Place –

Signature of Parent –

Date-

ANNEXURE 4

ABBREVIATIONS USED:

- AED – Anti-Epileptic Drug
- BP – Blood Pressure
- BZD – Benzodiazepines
- CNS – Central Nervous System
- HIE – Hypoxic Ischemic Encephalopathy
- PICU – Pediatric Intensive Care Unit
- LEV – Levetiracetam
- FPHT – Fosphenytoin
- SE– Status Epilepticus
- ILAE- International League Against Epilepsy
- PE- Phenytoin Equivalent

ANNEXURE 5

MASTER CHART

KEY TO MASTER CHART

S.No	PARAMETER	
	Previous seizure disorder	Y – Yes N – No
2	Previous AED	PBT – Phenobarbitone SVP – Sodium valproate
3	Etiology	SEP - Sepsis SD - New onset seizure disorder HIE - Hypoxic Ischemic Encephalopathy FSE - Febrile Status Epilepticus MEN Meningitis SDNC – Seizure Disorder Non Compliance of AED ACI - Acute CNS infection SDBS - Seizure Disorder Breakthrough Seizures SYN – Syndromic Association HYPO - Hypoglycemia
4	Type of seizures	F – Focal G – Generalized tonic clonic
5	Developmental History	AB – Abnormal N – Normal
6	ADR(Adverse drug reactions)	HT – Hypotension RD – Respiratory depression ATA – Ataxia BC(IC) – Behavioral changes (Irritable cry) THROM – Thrombocytopenia DEA - Death

FP																									
S.No	Name	Age (years)	Yr to mth conv	Age (month)	Total in month	age yr final	weight in Kg	prev sez disorder (Y/N)	AE drug taken	etiology	type of seizure	duration of seizure (min)	develop mental history	time drug adm to sz cessa	whether seizure terminated or not	recurrenc e	seizure free interval (hrs)	need of additiona l drug to terminat e present seizures	additiona l AED to terminat e present seizure	PICU stay in hr	total hospital stay (days)	ADR documented 1	ADR documen ted 2	ADR documen ted 3	ADR documen ted 4		
1	JAGADHEEP	0	0	6	6	0.5	4.5	Y	PBT	SEP	F	26	AB	0	N			Y	PBT	288	17	HT(IN)	RD(I)				
2	KOWSALYA	9	108		108	9	18	N		SD	G	18	N	3	Y	NR		N			3						
3	JHAMMED AMEERA		0	11	11	0.916666667	8	Y	PBT	HIE	G	31	N	1.5	Y	NR		N			3						
4	KATHIR	3	36	4	40	3.333333333	12	N		FSE	G	28	N	2	Y	NR		N		8	7						
5	VIBIN		0	8	8	0.666666667	5	N	SVP	HIE	G	17	AB	0	N			Y	PBT+MID	84	3	RD(I)	DEA				
6	MEGHA	0	0	5	5	0.416666667	3.4	Y	PBT	MEN	G	20	AB	0	N			Y	PBT+MID	18	0.75	RD(I)	DEA				
7	SATHRIYAN		0	6	6	0.5	5	N		FSE	G	21	N	3.5	Y	NR		N			5						
8	HEMA SHREE		0	11	11	0.916666667	7	N		SD	G	16	N	3	Y	NR		N		24	3						
9	SAI PRADAP	3	36	6	42	3.5	10	N		SD	G	22	N	2	Y	NR		N			3						
10	NITHISH	3	36		36	3	11	N		SD	G	18	N	4	Y	NR		N			3.25						
11	CHANDRU	3	36		36	3	12	N		SD	G	15	N	3.5	Y	NR		N		4	3						
12	EZHILRANI	4	48		48	4	15	Y	SVP	SDNC	G	23	AB	2	Y	NR		N		48	5						
13	KAVISH RAJA	7	84		84	7	20	Y	PBT	SD	G	26	N	1.5	Y	NR		N		20	3						
14	THILSATH BEEVI	11	132		132	11	25	N		SD	G	15	N	2.5	Y	NR		N		7	3						
15	VISHWA	3	36		36	3	10.2	N		FSE	G	24	N	3	Y	NR		N		24	4						
16	KAVYA	1	12	1	13	1.083333333	7	N		SYN	G	18	AB	3	Y	NR		N		16	7						
17	ANANYA		0	5	5	0.416666667	5	N		ACI	G	26	N	4	Y	NR		N		32	14						
18	SHANKAR	11	132		132	11	31	Y	SVP	SDNC	G	22	AB	3.5	Y	R	2H 28M	N		24	2						
19	UTHESH		0	4	4	0.333333333	3	Y	PBT	ACI	G	24	AB	0	N			Y	PBT+MID	23	1	RD(I)	DEA				
20	THILLAI RAJAN	1	12		12	1	8.5	N		ACI	G	18	N	3	y	R	50M	N		10	14	RD(NI)					
21	THARIKA	0	0	1	1	0.083333333	3.3	N		HG	G	26	N	2.5	Y	NR		N		51	14						
22	DINESH	1	12	6	18	1.5	7.5	Y	PBT	HIE	G	22	AB	2	y	NR		N			3						
23	YAMUNA	5	60	7	67	5.583333333	18.5	N		FSE	G	24	N	4	Y	NR		N		12	7						
24	KARTHIKEYAN	1	12	3	15	1.25	8.5	N		THULASI O(	G	18	N	5	Y	NR		N		104	16	ATA					
25	SADASIVAMN	11	132		132	11	38	Y	SVP	SDNC	G	19	N	4	Y	NR		N		7	2						
LC	LEVETIRACETAM																										
S.No	Name	Age (years)	Yr to mth conv	Age (month)	Total in month	age yr final	weight in Kg	prev sez disorder (Y/N)	AE drug taken	etiology	type of seizure	duration of seizure (min)	develop mental history	time drug adm to sz cessa	whether seizure terminated or not	recurrenc e	seizure free interval (hrs)	need of additiona l AED to control present seizure	additiona l AED to terminat e initial seizure	PICU stay in hr	total hospital stay (days)	ADR documented 1	ADR documen ted 2	ADR documen ted 3	ADR documen ted 4		
1	RAMKUMAR	3	36		36	3	12.5	Y	SVP	PMS	G	28	AB	4	Y	NR		N		25	4.5						
2	JITHESH	2	24	6	30	2.5	11	N		FSE	G	16	N	3.5	Y	R	13 H 22M	N		72	10						
3	ABISHEK		0	11	11	0.916666667	7	N		SD	G	17	N	4	Y	NR		N			3	BC(IC)					
4	SIVAPRIYA		0	8	8	0.666666667	5.8	N		ACI	G	15	N	4.5	Y	NR		N		70	10						
5	VINITH	1	12	6	18	1.5	9	N		CRS	G	26	AB	4	Y	NR		N		24	5						
6	SAIKARTHIKEYAN	1	12	3	15	1.25	8	Y	SVP	HIE	G	23	AB	3	Y	NR		N			3						
7	MAHESH	1	12	1	13	1.083333333	10	N		SD	G	21	N	2.5	Y	NR		N			3						
8	PREETHI	4	48		48	4	15	N		ACI	G	24	N	0	N			Y	PBT	98	14	RD(NI)					
9	DHIVAN	2	24		24	2	11	N		SD	G	18	N	3.5	Y	NR		N		22	11						
10	HARISH		0	7	7	0.583333333	5	N		SD	G	31	N	4	Y	NR		N			4						
11	LOGANAYAKI	4	48	6	54	4.5	15	Y	SVP	SDNC	G	28	AB	4.5	Y	R	25 M	N		48	7						
12	HARISH		0	6	6	0.5	4.5	N		HIE	G	24	AB	3.5	Y	NR		N			4						
13	KAVINESH	1	12	4	16	1.333333333	7.5	N		FSE	G	18	N	4	Y	NR		N			5						
14	FAZIL	8	96		96	8	21	Y	SVP	SDBS	G	17	N	3	Y	NR		N			2						
15	KANISH		0	4	4	0.333333333	4	N		ACI	G	22	N	4	Y	NR		N		12	13	THROM					
16	JEEVANSHREE	1	12		12	1	7	N		CAMPHOR	G	29	N	2	Y	NR		N			1						
17	ROSHAN	1	12	6	18	1.5	10	N		ACI	G	20	N	3	Y	NR		N		28	10						
18	YOGESHWARI	3	36	3	39	3.25	12	N		SD	G	16	N	4	Y	NR		N			3						
19	MUTHUMANI		0	4	4	0.333333333	5	Y	PBT	HIE	G	18	AB	4	Y	R	1 H 30 M	N		44	5						
20	HARIVARSAN	6	72	6	78	6.5	30	N		FSE	G	31	N	4	Y	NR		N			10						
21	SASIDHARAN		0	5	5	0.416666667	4.8	Y	PBT	HIE	G	19	AB	3.5	Y	NR		N			5						
22	ABDUL FAIZ		0	11	11	0.916666667	9	N		ACI	F	25	N	0	N			Y	PBT+MID	72	3	RD(I)	HI(INO)	DEA			
23	ANBUSELVI		0	10	10	0.833333333	6.5	N		FSE	G	24	N	3	y	NR		N		15	10						
24	EBSHIBA	7	84		84	7	18	Y	SVP	HYPO	G	26	N	4	Y	NR		N			3						
25	YAZHINI	3	36	3	39	3.25	12	N		ACI	G	17	N	3.5	Y	R	18 M	N		42	10						